ASSESSING THE RISK OF CHEMOTHERAPY TOXICITY AND HOSPITAL ADMISSION DUE TO TOXICITY

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Assessing the risk of chemotherapy toxicity and hospital admission due to toxicity

A study of acute chemotherapy toxicity and related hospital admission in a large UK teaching hospital, based on proactive telephone assessment patients.

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Abstract

Introduction: Acute chemotherapy toxicity is common and can have negative effects for the patient and health economy and hospitalisation can be necessitated.

Aims: To identify the incidence of toxicity and admission, and predictors of toxicity occurrence, severity, hospitalisation and length of stay.

Method: Data was obtained from a proactive telephone assessment of acute toxicity 24 hours after administration of a first cycle of chemotherapy to patients in a large UK NHS teaching hospital.

Results: 1539 patients were studied and the overall incidence of toxicity was 35.6% (530 patients). Disease site and number of chemotherapy agents given were shown to predict toxicity, with breast and upper gastrointestinal cancers having a higher likelihood of toxicity. Disease was predictive of toxicity grade, with urology, gynaecology and lung cancer patients experiencing higher grades of toxicity than other tumour sites. The rate of hospital admission due to toxicity was 13.1% (203 patients) and median length of stay 3 days (1-28). The risk of admission had some risk factors in common with toxicity. Disease and the number of drugs in the regimen affected the risk of admission, with gynaecology, head and neck and lung cancer patients and patients who received 3 drugs having a higher likelihood of admission. Predictors in the sub-groups of breast, colorectal and lung cancer patients did not differ greatly from the whole population and the number of drugs was shown to be a predictor of nausea, vomiting and fatigue when explored as secondary outcomes.

Conclusion: The research partly addressed the main aim and highlighted areas where further research is required.

Keywords

Cancer, chemotherapy, toxicity, hospitalisation, nausea, vomiting, fatigue

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Glossary of terms and abbreviations

ADL – Activities of Daily Living

ATP – Adenosine Tri-Phosphate

5HT/5HT3 – 5-Hydroxytryptamine

AE – Adverse Effect

ASCO – American Society of Clinical Oncology

BNF – British National Formulary

BRCA ½ - BReast CAncer susceptibility gene

CATT – Cancer Admissions and Triage Team

CDF – Cancer Drugs Fund

CINV – Chemotherapy Induced Nausea and Vomiting

CNS – Central Nervous System

CUP – Cancer of Unknown Primary

CRASH – Chemotherapy Risk Assessment for High Age Patients

CRG – Clinical Reference Group

CTCAE – Common Terminology Criteria for Adverse Events

DNA – Deoxyribonucleic Acid

ECOG – European Cooperative Oncology Group

EGFR – Epidermal Growth Factor Receptor

ESMO – European Society of Medical Oncology

FDA – Food and Drug Administration

FEC/FEC75/FEC100 – Fluorouracil, Epirubicin, Cyclophosphamide (chemotherapy regimen)

GI – Gastrointestinal

HPA – Hypothalamic-Pituitary-Adrenal

HR – Hazard Ratio

HRA – Health Research Authority

IRAS – Integrated Research Application System

IT – Information technology

MAB – Monoclonal Antibodies

MASCC – Multinational Associate of Supportive Care in Cancer

MAX-2 – A tool to calculate risk of toxicity

MDT – Multi-disciplinary Team

mTOR – Mechanistic Target of Rapamycin

NCEPOD – National Confidential Enquiry into Patient Outcomes and Death

NCI – National Chemotherapy Institute

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NK – Neurokinin

NRES – National Research Ethics Service

NSCLC – Non-Small Cell Lung Cancer

NTS – Nucleus of the Solitary Tract

NUH – Nottingham University Hospitals

PS – Performance Status

REC – Research Ethics Committee

RR – Relative Risk

SACT – Systemic Anticancer Therapy

SD – Standard Deviation

SN38 - 7-Ethyl-10-hydroxycamptothecin

SN38G 7-Ethyl-10-hydroxycamptothecin Glucoronide

SPSS – Statistical Package for Social Sciences

TKI – Tyrosine Kinase Inhibitor

TNF – Tumour Necrosis Factor

UK – United Kingdom

UKONS – United Kingdom Oncology Nurses' Society

US – United States of America

USD – United States Dollars

1.0 Introduction

In the United Kingdom in 2011, more than 331,000 cases of cancer were diagnosed (Cancer Research UK, 2014). This equates to 524 cases per 100,000 people. Since the mid-1970s this incidence has increased by more than 23% in males and 43% in females. There are many treatment options available for cancer using different modalities (such as chemotherapy, radiotherapy, surgery and hormonal therapy) and many different technologies. The modality of interest is chemotherapy, defined as systemic pharmacotherapy for cancer indications.

1.1 Chemotherapy

The term “chemotherapy” is defined by the NCI dictionary of cancer terms as:

“Treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated. It may be given alone or with other treatments, such as surgery, radiation therapy, or biologic therapy.” (National Cancer Institute, 2018)

In clinical practice it includes cytotoxic chemotherapy as well as targeted therapies including monoclonal antibodies and other biologic agents. Most anticancer agents act on cell division and thus interfere with cell replication and cancer proliferation (Neal and Hoskin, 2009). This is by a variety of mechanisms. Many drugs interfere with DNA replication or repair, others directly act on mitosis whereas others reduce tumour vasculature. Targeted agents often work on cell signalling pathways. Immunotherapies use a variety of mechanisms that induce destruction of cancer cells by the immune system (National Cancer Institute, 2018). All agents are associated with some degree of toxicity, as is any drug. The term systemic anticancer therapy (SACT) is regularly used in practice to include chemotherapy and targeted therapies for cancer.

In England, between July 2013 and June 2014, well over 154,000 patients received drug treatment for cancer (Chemotherapy Intelligence Unit, 2014). This is a large number of patients and represents a significant burden of disease. According to Cancer Research UK, in 2013/14, 28% of patients diagnosed with cancer, received chemotherapy (Cancer Research UK 2015d). A national dataset of chemotherapy now exists in the UK and records 43 data fields around each cycle of chemotherapy, which must be submitted for national review (NHS England, 2018). The dataset is currently producing basic reports of the national picture in the UK. In 2014, breast cancer was the cancer most commonly treated with chemotherapy, followed by lower gastrointestinal (GI) and lung cancer.

1.1.1 Commissioning of Chemotherapy

In England, the main provider of chemotherapy is the National Health Service (NHS). Within the NHS, chemotherapy is considered a specialised service and so is commissioned by NHS England (Staines *et al*., 2014). All commissioning decisions are therefore made on a national level, under guidance from the Chemotherapy Clinical Reference Group (CRG). The National Institute for Health and Care Excellence (NICE) considers all new and emerging therapies. NICE can either decide to enter a new therapy into baseline commissioning or to fund a therapy under the Cancer Drugs Fund (CDF), which was established in 2010 and funds new and innovative cancer treatments (Department of Health, 2011).

1.1.2 Toxicity

Chemotherapy is known to be commonly associated with various toxicities of different grade, type and significance, since chemotherapeutic agents are rarely totally selective for cancer cells. These toxicities can require interventions ranging from self-care to critical care admission and it is generally accepted that chemotherapy toxicity necessitates the use of high levels of healthcare resource.

Local experience suggested that a large proportion of toxicities is experienced with the first cycle of chemotherapy and this is supported by Extermann *et al.*, who pooled several studies of chemotherapy in different diseases, that found a greater proportion of toxicity in the first cycle (Extermann *et al*., 2012).

As part of an initiative to reduce the number of readmissions to hospital of oncology patients at Nottingham University Hospitals (NUH), various measures have been put in place. One such measure was to establish the cancer admissions and triage team (CATT), which is a team of nurses who work to

reduce cancer admissions. The CATT team is a team of specialist nurses who run a variety of initiatives and were employed in 2014, as part of the wider acute oncology service at NUH. The acute oncology service aims to improve the care of patients admitted with oncological emergencies, many of which are a result of chemotherapy toxicity. The CATT team enabled further improvements to be made by adding the required resource to the team. The CATT nurses are responsible for managing oncology inpatient flow at NUH and monitor inpatients, especially on non-oncology wards to ensure timely senior review. The CATT team also staff the 24 hour rapid response telephone line that patients are encouraged to use when on chemotherapy, should they experience any difficulty or have any questions.

One scheme facilitated by the CATT team was started in January 2015 and is a chemotherapy telephone assessment service. The day following the administration of a first cycle of chemotherapy, every patient receives a telephone call where an assessment of chemotherapy toxicity is undertaken. The standard operating procedure for the telephone service is included in Appendix 1. The standard operating procedure is based on the UKONS oncology/haematology 24 hour triage tool, which is the tool employed by the CATT team nurses when taking triage calls from chemotherapy patients (Jones *et al*., 2010). Advice can be given in order to facilitate self-management of toxicity and referrals made as needed. Depending on the needs of the patient and the chemotherapy regimen, a further call is arranged in a few days' time to assess the progress of the patient. The nurses can arrange medical assessment for the patient or hospital admission if required for treatment of a toxicity.

1.2 Literature Review

A thorough literature search was conducted in order to identify what was already known about chemotherapy toxicity and the factors influencing it. A scoping literature review was utilised due to the broad nature of the subject matter. In many cases, the literature around certain subjects was sparse, meaning that a more in-depth review such as a systematic review or meta-analysis could not be employed. The key aim of the review was to identify the gaps in the data and it was felt that a scoping review would best achieve this. Medline® and EMBASE® databases were used for the search, which followed a defined search strategy (shown in Appendix 5). The search strategy highlights the systematic nature of the review. Papers® (Mekentosj BV) was the reference management system chosen to organize references. Where possible thesaurus or controlled vocabulary (such as MeSH) search terms were used and if large amounts of data were identified, restrictions were applied to filter data found in certain fields such as the title. Randomised controlled trials and meta-analyses were preferred but not always found. No date limits were applied. The literature review was originally conducted in 2015 at the time of writing the research proposal. It was repeated in 2018 at the time of writing up the thesis, to identify any new evidence.

1.2.1 Incidence

Finding data on the overall incidence of toxicity in patients on chemotherapy, across all tumour sites and treatments did not prove possible. This probably reflected the heterogeneous nature of chemotherapy and would require a number of systematic reviews across different diseases and treatments in order to fully clarify the wider picture. Different chemotherapies used in different diseases all carry distinct sets of toxicities. A 2008 UK report looked at deaths within 30 days of receiving systemic anti-cancer therapy (SACT). It was noted that 43% of patients who had died within 30 days of receiving SACT had experienced a grade 3 or 4 toxicity according to CTCAE (common terminology criteria for adverse events) criteria related to their treatment (Mort *et al*., 2008). CTCAE criteria are commonly used in clinical practice to grade the severity of

toxicity. Toxicity is classified according to the toxicity being described, however the general rule is thus:

Grade 0 = no toxicity

Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 = Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grader 3 = Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL

Grade 4 = Life-threatening consequences; urgent intervention indicated

Grade 5 = Death related to AE

(National Cancer Institute, 2010)

Mort *et al.* performed this observational study using voluntary questionnaire completion by UK hospital trusts so may not have been representative of the worldwide population. However, it did suggest an association between high-grade toxicity and death of chemotherapy patients. Sophisticated statistical analysis was not applied and so it was difficult to use the report as anything other than a snapshot review, which was used in the UK to highlight concerns around the safety of cancer chemotherapy.

Reporting of toxicity relies on patients reporting their experience to healthcare professionals. This can be done in a variety of different ways, from reporting in the clinic, to using technology to report. A single-centre study of patient reported outcome measures in 71 patients with breast, colorectal and upper GI cancers reported surveyed chemotherapy toxicity (Jenner *et al.*, 2010). Surveys were completed by patients without healthcare professional intervention, prior to each cycle of chemotherapy. High rates of questionnaire completion were seen. Grade 3 or 4 toxicities were seen in 21 (29%) of patients but an overall toxicity rate was not reported. It was felt that the method

of assessment empowered and informed patients and allowed for real-time reporting of symptoms and could be used to structure clinic reviews.

1.2.2 Economic Effects

A search looking at the economic effects of toxicity only revealed very specific literature, relating to specific drugs or specific patient groups, which suggested that the overall economic impact of chemotherapy toxicity may not be fully understood and would be difficult to describe. A German study looked at chemotherapy toxicity in patients with lymphoproliferative disorders and non-small cell lung cancer (NSCLC) (Paessens *et al*., 2011). All interventions associated with toxicity including drug treatment, laboratory tests and necessary scans were included in the study. Of the 1004 cycles of chemotherapy looked at, 50% were associated with a grade 3 or 4 toxicity. A mean value for toxicity related costs of €1032 per cycle (2007 euro value) is reported. Costs rose exponentially with the grade of toxicity and those associated with infection requiring intensive care were higher. Those cycles associated with 4 or more toxicities had the highest costs associated with them. Whilst this was a useful study, it was limited to two very specific disease states and looked only at one healthcare economy, so it is difficult to extrapolate it to other populations. However, it identified that significant costs are associated with chemotherapy toxicity.

Latremouille *et al.* looked at 4158 patients with metastatic colorectal cancer who had had at least one treatment episode over a 5 year period, from an administrative claims database (Latremouille-Viau *et al*., 2017). Haematological adverse effects of treatment had an average cost of $1480USD, respiratory $1253USD, endocrine/metabolic $1213USD, central nervous system $1136USD and cardiovascular $1036USD. This study was in US practice only and so may not be applicable to UK practice.

A 2016 retrospective study of 729 patients with metastatic breast cancer looked at patients receiving biologic or chemotherapy with or without endocrine therapy (Irwin *et al*., 2016). The analysis found that the average treatment related healthcare costs in this population for haematological toxicities were $1524USD per patient per month, with neutropenia or leucopenia costing an average of $550USD and anaemia $942USD. Gastrointestinal adverse effects costed an average of $839USD. Adjusted all-cause monthly costs increased with the number of adverse effects, with the average cost for patients with >7 adverse effects being $19,701USD, compared to $5908USD for patients reporting no adverse effects ($p<0.01$). This clearly demonstrated that toxicity is associated with higher healthcare costs, although the study was limited to one tumour site treated within one healthcare economy, so may be difficult to apply to NHS practice. It did however provide similar costs for haematological adverse effects as Latremouille *et al.*, suggesting adverse effect costs may be similar across different disease states.

1.2.3 Effects of Toxicity

Various studies have highlighted the potential effects of toxicity on patients and disease, including need for dose reduction, discontinuation of chemotherapy, effects on clinical trials and even death (Kalsi *et al*., 2014; Mort *et al*., 2008). An observational study in a London hospital found that early treatment discontinuation was required in 23 (21.3%) of elderly patients receiving chemotherapy for various cancers due to toxicity (Kalsi *et al*., 2014). The NCEPOD report (Mort *et al.* 2008) could be interpreted to suggest that toxicity increased the risk of death, however there was no ratified statistical evidence of this in this report and indeed this is not what the report set out to be able to prove. It did mention that toxicity assessment was not always recorded, with documented toxicity assessment being seen in only 170 (64%) of cases and a toxicity checklist being used in only 26 (10%) of cases.

There was conflicting data, with some sources stating that toxicity can predict outcomes in certain sub-groups, namely breast cancer, osteosarcoma and

colorectal cancer (McTiernan *et al*., 2012; Chintamani *et al*., 2004; Klepin *et al*., 2014; Schuell *et al*., 2005; Rambach, 2014). A group looking at chemotherapy in patients with localized extremity osteosarcoma over a long period of time concluded that chemotherapy toxicity predicts survival in this sub-group. This used a multivariate analysis and showed that differing toxicities of differing grades predicted survival (McTiernan *et al*., 2012). Chintamani *et al.* suggested that toxicity in breast cancer in the neo-adjuvant setting (chemotherapy given prior to another intervention such as surgery, with a curative intent) predicts response (Chintamani *et al*., 2004). This was a small study in a very specific patient group and so it was difficult to extrapolate to other areas. It was also intensive chemotherapy with curative intent and this is likely to have had an effect on the level of toxicity experienced. Indeed contradictory evidence was shown in patients with breast cancer where toxicity of grade 3-5 was not thought to have an effect on overall survival (Klepin *et al*., 2014). A further study claimed that toxicity can be used as a predictor of survival in patients on chemotherapy for colorectal cancer (Schuell *et al*., 2005). Univariate and multivariate analyses revealed toxicity as an independent prognostic indicator. It was claimed that the occurrence of just one adverse event, increases the incidence of response or stable disease by 34%. The correlation between toxicity and therapeutic benefit was noted despite type and degree of toxicity. Further French evidence supports the theory of toxicity predicting survival in colorectal cancer (Rambach, 2014). A retrospective analysis of 399 patients who received chemotherapy for metastatic colorectal cancer in a 10-year period concluded that the occurrence of neutropenia or thrombocytopenia in the first or second cycle of chemotherapy predicts better survival. In contrast, anaemia during chemotherapy was associated with a poorer overall survival. It could be theorised that the occurrence of particular toxicity is due to effects of chemotherapy on non-malignant tissue and as such could be an indicator of the effect of that therapy on malignant tissue. This required careful consideration in this research.

A small Canadian study looked at how the risk of chemotherapy toxicity affected patient preferences with respect to choosing chemotherapy regimens (Beusterien *et al*., 2014). 102 women were asked to complete a single web-

based questionnaire to elicit preferences for 17 grade 1-4 toxicities associated with available chemotherapies. A 5% reduction in the risk of grade I – II sensory neuropathy, nausea and motor neuropathy had the highest influence on patient preference. Grade III-IV motor neuropathy, nausea and vomiting and myalgia made the most difference for more severe grades of toxicity. Patients were willing to receive an intravenous regimen as opposed to an oral regimen in order to avoid a 5% increase in the risk of the majority of toxicity. Although this did not comment on toxicity occurrence, it did give an insight into the opinions of patients with regards to toxicity. Of course this is one patient group in one centre.

A 2005 breast cancer trial was forced to close a high dose arm early due to toxicity (Brain *et al*., 2011). High rates of skin toxicity (32.4% rate of grade 3 /4 toxicity) were reported in the high dose arm of this randomized phase II trial, which investigated the sequential approach of anthracycline and taxane based adjuvant chemotherapy in patients with high risk breast cancer. This study highlights the problematic nature of toxicity and highlights the potential effects on trials and potentially curative chemotherapy.

A 2017 study investigated 766 patients with metastatic malignancies in a single centre (Basch *et al*., 2017). Patients were assigned to self-record a toxicity assessment on a tablet or to usual care. Once reported on the tablet, toxicity details were made available to physicians caring for the patient. It was found that median overall survival was 5 months longer in those patients who self-reported toxicity, leading the authors to conclude that systematic self-reporting of toxicity confers a survival advantage. Of course many factors affect survival, but the authors stated that a multivariable model produced statistically significant results.

1.2.4 Hospitalisation

Acute, unplanned admission to hospital was considered. General literature around acute hospital admission was reviewed in addition to literature around admission due to chemotherapy toxicity.

A French study looked at 2692 hospital admissions to French hospitals over a six-month period (Bénard-Laribière *et al*., 2015). It was found that 97 (3.6%) of admissions were due to an adverse drug reaction. Older patients were significantly more likely to experience an adverse drug reaction than younger patient ($p<0.001$). Antineoplastic agents were responsible for 12 (12.6%) of adverse drug reaction related admissions. The authors used their data to predict the rate of admission across France. It may be possible to do this for other healthcare systems, but consideration would need to be given to differences in healthcare systems between nations.

A longitudinal study of lung cancer patients found that more admissions were due to disease than treatment effects (Cuppens *et al*., 2016). The study looked at all unplanned hospital admissions in a single tertiary centre in a 6-month period. Two hundred and seven admissions were seen and mean length of stay was 9.5 days (SD not stated). The study found that patients with a poor performance status, uncontrolled cancer and cancer related events had worse outcomes. This is a single centre study in a specific population so is not generalizable to a wider population as there may be differences in local practice that this would not account for and other populations could have other differences such as socioeconomic variance and different ethnicities.

Another single-centred longitudinal study of elderly patients found that mortality was higher in patients with a primary diagnosis of cancer (Walsh *et al*., 2012).

A 2017 American review of hospital admissions in patients with prostate cancer found that patients with prostate cancer were more likely to be admitted to hospital than their peers who did not have a diagnosis of prostate cancer and were also more likely to have recurrent admissions (Gnanaraj *et al*., 2017). Co-morbidity with congestive heart failure and the presence of metastases were found to be risk factors for admission. This study was specific to the diagnosis of prostate cancer and so is not generalizable to a wider population.

A large study of elderly patients representative of community-dwelling individuals found that impairment of activities of daily living were twice as likely to be admitted to hospital as those without impairment (Aliyu *et al*., 2003). This study was not specific to cancer and chemotherapy but suggested that functional status does affect the risk of hospital admission.

Various factors affecting length of stay were identified in 1996 by Clarke (Clarke, 1996). Although a dated review, it suggested some reasons for variation in length of stay in hospital that are applicable to current clinical practice. The review was also around admissions for any reason, so is not directly applicable to chemotherapy toxicity, but some useful information was gained from the analysis. Clarke suggested that there is often a geographical variation in length of stay, with length of stay varying between different countries and healthcare systems. The other reasons cited for variations in length of stay were categorised as supply factors and demand factors.

- Supply factors
    - Individual practice style
    - Discharge policies; level of illness at which hospital care is considered desirable
    - Bed supply, hospital competition and the quality and availability of primary, community or convalescent care
    - Method of payment – prepayment or fee for service
- Demand factors
    - Socioeconomic status

- Disease severity
- Comorbidity
- Direct or indirect costs to patients or their carers

Clarke analysed several reviews, which included thousands of patients to establish the above factors. These were of clinical relevance and pertinent to this research.

Little data was found regarding hospitalisation due to chemotherapy toxicity. This suggests that it has not been studied widely within the context of published literature. This helps to justify the reason for undertaking this research. Some data was seen around hospitalisation in studies looking at other aspects of toxicity but no studies were seen that looked at the risk of hospital admission specifically due to toxicity. Data on a wider cancer patient population looking at admission was not found, suggesting that this is an area of interest for future research.

1.2.5 Predicting Toxicity

Two fairly large studies were found looking at predicting chemotherapy toxicity, both of which have aimed to produce predictive tools (Extermann *et al*., 2004; Extermann *et al*., 2012). The tools each used a number of factors to predict toxicity, some of which were common to both tools. Both patient and treatment factors were considered. One tool looked only at older patients and considered a large number of different chemotherapy regimens, whereas the other looked at a wider age range but within a much more limited number of regimens.

A prospective, multi-centre study was conducted assessing toxicity in 582 patients over 70 years of age using 24 parameters (Extermann *et al*., 2011). The authors developed their own predictive score called the Chemotherapy Risk Assessment Score for High Age patients (CRASH). They also divided into sub scores for haematological and non-haematological toxicity. The score classifies patients as low, medium-low, medium-high and high risk of toxicity.

The score uses haemoglobin, creatinine clearance, albumin, self- rated health, Eastern Cooperative Oncology Group (ECOG) performance, Mini-Mental Status score, Mini-Nutritional Assessment score, and Chemotox as predictors of toxicity. A bootstrap internal validation and independent sample validation demonstrated stable risk categorization, meaning that the score could be used effectively to predict the risk of toxicity. An aim of the study was to develop a score that could be used across all regimens. The score uses a combination of patient and treatment factors to predict overall toxicity risk. The MAX-2 method was used to calculate regimen toxicity risk. The study looked at 121 different chemotherapy schedules and various different diseases. This study gives a reliable, tested predictor for elderly patients, however the study population was only recruited from 4 centres in a similar area, so generalization to other populations may be difficult, due to potential differences in populations such as ethnicity or socioeconomic status.

The MAX-2 index is of particular interest and is very pertinent to this research. The MAX-2 index was developed as a predictor of toxicity, and combines both patient and chemotherapy factors when calculating risk. MAX-2 uses the most frequently reported haematological toxicity and the most frequently reported non-haematological toxicity to come up with a risk score for overall toxicity of a regimen (Extermann *et al*., 2004). Extermann *et al.* decided to test the MAX-2 index on a large scale and so used the ECOG trial database to do this. Four trials were included in the review, which included 2515 patients eligible for analysis. 410 (16%) of patients were over 70 years old and 12 different treatment regimens were tested, which were quite different in nature. The trials were for breast, lung and bowel cancer. A simple linear regression model and a logistic regression analysis were used. The prevalence of toxicities was looked at in each study and the MAX-2 score calculated. The regression models were then used to evaluate the association of the MAX-2 index with the percentage of patients experiencing at least one grade 4 haematological or one grade 3 or 4 non-haematological toxicity. The MAX-2 index was found to have a high association with the global incidence of severe toxicity. The authors concluded that the MAX-2 index is a reliable way of summarizing the toxicity form a chemotherapy regimen on a per patient basis. They stated that the index would

be very helpful in comparing the toxicity of several chemotherapy regimens. This could be applied to this research, as although the authors claimed to have validated MAX-2 there are still many regimens and patient groups that it has not been tested in, and there is more work that could be done to look at various sub-group analyses.

Hurria *et al*. looked at 500 chemotherapy patients aged 65-91 years and suggests that the risk of toxicity increases with increasing age (Hurria *et al*., 2011). They demonstrated that 115 (23%) of patients were admitted during treatment, although it is not known if this was due to chemotherapy toxicity. A predictive model for toxicity was developed using: geriatric assessment variables; laboratory test values; patient, tumour and treatment characteristics. The score was then used to stratify patients as at low, intermediate or high risk of toxicity. Several risk factors for toxicity were identified and confirmed as clinically significant. These included age over 72 years, cancer type (gastrointestinal or genitourinary), standard dosing of chemotherapy, poly-chemotherapy, haemoglobin (males < 11 g/dL; females <10g/dL), creatinine clearance less than 34 mL/min, hearing impairment described as fair or worse, greater than or equal to one fall in the last 6 months, limited in walking one block, need for assistance in taking medications, and decreased social activities because of physical or emotional health. This study was of interest as it described factors influencing the occurrence of toxicity.

A 2016 study of 1463 patients receiving capecitabine based chemotherapy found that 234 (16%) of patients experienced an early-onset grade ≥3 toxicity (Meulendijks *et al*., 2016). Authors found that renal function carried an odds ratio of experiencing a grade ≥3 toxicity of 0.85 per 1.73ml/min/1.73m (p=0.0007 95% CI 0.78-0.94), body surface area 0.33 per m^2 (p=0.0053 95% CI [0.15-0.72]), and age 1.14 per decade (p=0.0891 95% CI [0.98-1.34]). Age was also found to be significantly associated with fatal treatment-related toxicity with an odds ratio of 5.75 (p=0.0008). The authors suggested that age, renal function and body surface area can all be used as predictors of capecitabine toxicity. It was not possible to know if these predictors would also apply to other

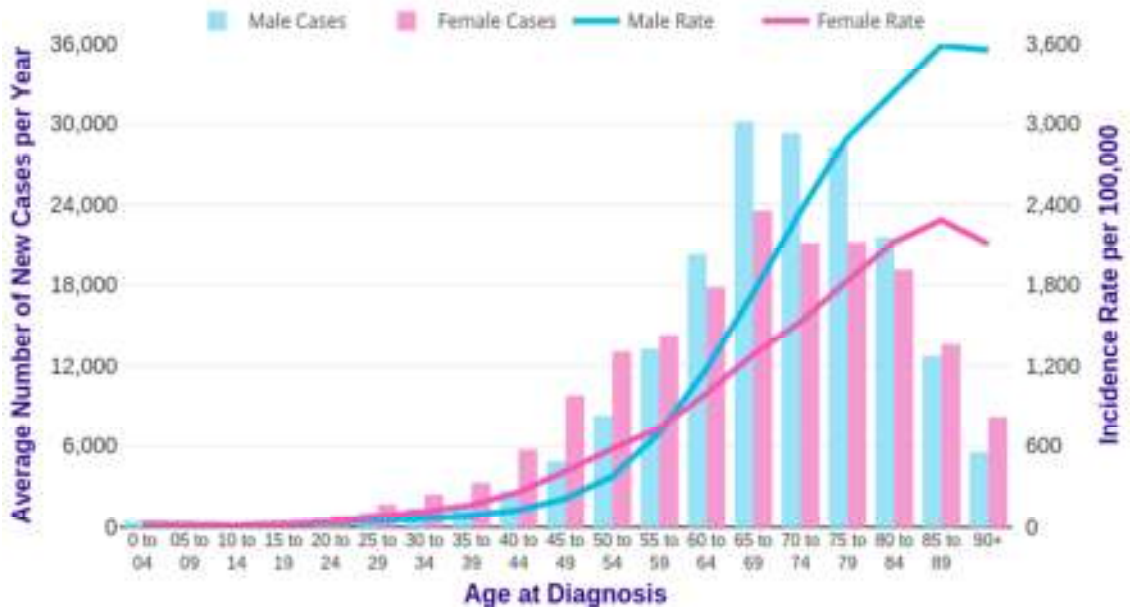
antineoplastic agents.

Chase *et al.* used a logistic regression model to look at specific predictors of grade 3 or 4 toxicity in patients undergoing chemotherapy for advanced or relapsed cervical cancer (Chase *et al*., 2015). Six hundred and seventy three patients were considered. Higher performance status predicted grade 3 or 4 toxicity with an odds ratio of 2.78 (95% [CI 1.66-4.68]). Exposure to previous radiation and treatment regimen were associated with the reporting of grade 3 or 4 leucopenia ($p<0.05$) and anaemia ($p<0.005$). Performance status and treatment regimen were associated with the development of grade 3 or 4 thrombocytopenia ($p<0.05$). Age and treatment regimen were associated with the development of 3 or 4 neutropenia ($P<0.05$). The study was confined to single tumour site so may not be applicable to all treatments, however it did give an indication of the factors that may predict toxicity.

1.2.6 Patient Factors

1.2.6.1 Age

The risk of cancer increases with age. Figure 1 illustrated the incidence of cancer in the UK.



(Cancer Research UK, 2015e)

Figure 1. Incidence of Cancer in the UK (2013-14)

This shows that cancer incidence increases with age and there is a sharp rise in incidence at 55-59 years. Highest rates are seen in people over 75 years old. Cancer incidence does not necessarily correlate with chemotherapy usage, as not all patients with cancer will receive chemotherapy for a variety of reasons. As the above graph includes all cancer diagnoses, many patients will receive a different treatment modality and some patients may receive no treatment at all.

It is well documented that there are changes in physiological processes that occur with age. Balducci and Extermann argue that the most consequential changes that occur are in volume of distribution and renal excretion of drugs (Balducci and Extermann, 2000). Volume of distribution decreases with age for water-soluble drugs and can predispose patients to toxicity. Renal function decreases with age and this can reduce excretion of drugs excreted by this route, resulting in more toxicity. These principles apply to chemotherapy. It is also thought that changes in the hepatic metabolism of drugs changes with age, although the exact effects on chemotherapy are not well documented. Tissue may be more susceptible to the effects of chemotherapy in older

patients. Older patients have a lower stem cell reserve, so are more susceptible to haematological toxicity. They also have a reduced ability to catabolise cytotoxic drugs and repair cell damage caused by these agents. There is a critical reduction in functional tissue in older patients so that damage to these tissues may be of greater consequence than in younger patients who have a higher reserve.

It has been suggested that older patients derive the same benefit from chemotherapy as younger patients (Muss *et al*., 2005). A multivariate analysis of 6487 patients with breast cancer who received chemotherapy, found that disease free survival was not affected by age. It was, however, shown that younger patients had a longer overall survival, and older patients had a 1.5% higher treatment related mortality. This study only focussed on breast cancer, but the potential effect of age on outcomes of chemotherapy is of interest. In a further analysis of patients with node positive breast cancer, treated with chemotherapy, Muss suggests that older patients again derived the same benefit from chemotherapy as younger patients in a review of 6642 patients across 3 trials (Muss *et al*., 2007). Older patients had a significantly higher rate of grade 4 haematologic toxicity but no difference was found in the incidence of grade 3 to 4 non-haematologic toxicities. This study is of interest to this research, but is limited to one tumour site, which limits the treatments used and also only reports grade>3 toxicity.

A combined analysis of phase III clinical trials in metastatic colorectal cancer found that older patients derived the same degree of benefit from the addition of irinotecan to 5-fluoruracil and folinic acid as younger patients (Folprecht *et al*., 2008). The study found that in general, older patients did not have a higher incidence of toxicity than younger patients, with the exception of hepatotoxicity, however repeat of their regression model with age as a continuous variable did not confirm these findings. Older patients were also found to have a greater risk of sever neutropenia. As with the Muss study, this paper only included patients with a single diagnosis, so extrapolation to a whole population is not possible (Muss *et al*., 2007).

Other studies have identified interesting facts about the effect of age on toxicity. Nie *et al.* validated the tool developed by Hurria *et al*., in 120 lung cancer patients (Nie *et al.* 2013) and Reinsich *et al.* suggested that the range and intensity of toxicity increases with age in breast cancer (Reinisch *et al.* 2013). Kalsi *et al.* found that dose reduction of chemotherapy was required frequently in elderly patients (Kalsi *et al*., 2014). Dose reduction due to toxicity was required in 60 (55.6%) of patients, 21(35%) of whom had a maximum grade 2 toxicity. Treatment was discontinued early in 23 (21.3%) of patients, 8 (39.1%) of whom had no greater than a grade 2 toxicity.

A review of 65 elderly patients on chemotherapy, led Wildes *et al*. to conclude that performing a geriatric assessment prior to chemotherapy is associated with completing a planned number of cycles of chemotherapy (Wildes *et al*., 2013). The authors drew several conclusions from their data around the factors influencing the completion of treatment. No control was used in this trial and sub groups contained very small numbers of patients. The study found that 20 (31.1%) of patients experienced a grade 3 or 4 non-haematologic toxicity and curative intent therapy, ECOG performance status 2-3 and renal function were associated with therapy completion.

LoConte *et al.* found that age is not predictive of dose limiting toxicity in phase I clinical trials of chemotherapy (LoConte *et al*., 2009) . This was a small study in a very specific group of patients and patients chosen for clinical trials may be required to fulfil criteria that may not be applicable to a wider population.

Balducci and Extermann suggested in a review of a number of prior studies, that increasing age increases the reporting of a number of toxicities including myelosuppression, mucositis, cardiodepression, peripheral neuropathy and central neurotoxicity (Balducci and Extermann, 2000). A number of trials of

differing design were included in the review and pointed towards age as a predictor of toxicity.

A study of all breast cancer trials open in a Canadian cancer centre between 1999 and 2012 looked at 799 patients (Mariano *et al*., 2015). Older and younger patients experienced similar numbers of toxicities, however the older patients were more likely to be enrolled in endocrine or bone related treatment arms and younger patients more likely to receive chemotherapy. A multivariate analysis showed that treatment type was the strongest predictor of toxicity and of the patients receiving chemotherapy, there was no difference in incidence of toxicity. This contradicted other evidence which suggested that toxicity increases with age.

In a small study of breast cancer patients, Dees *et al.* found that there appeared to be no difference in haematological and non-haematological toxicity incidence between older and younger patients, but this study only looked at 44 patients and so it was difficult to extrapolate these results to a larger population (Dees *et al*., 2000).

1.2.6.2 Co-morbidity

No specific literature was found pertaining to the effect of Karnofsky or ECOG performance status on toxicity (Oken *et al*., 1982). Performance status is a tool used in clinical practice as a quick assessment of the overall health and functional status of a patient (Oken *et al*., 1982). At NUH, the ECOG performance status is recorded prior to each cycle of chemotherapy prescribed. **Table 1** shows the definition of each grade of the performance status, as described by Oken *et al.*

Table 1. ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

In 2009 a national report was produced by the National Confidential Enquiry into Patient Outcomes and Deaths, which looked at patient deaths within 30 days of chemotherapy (Mort *et al*., 2008). The authors stated that the use of palliative chemotherapy in patients with a performance status of 3 or 4 should be done so with caution and after discussion with the multidisciplinary team (MDT).

Performance status has been shown to affect survival in different cancer diagnoses (Kelly and Shahronki, 2016). Several large studies have suggested that the patients with a lower performance status have a longer duration of survival than those whose performance status is greater than 1 (Simmons *et al*., 2015; Stone and Lund, 2007; Kao *et al*., 2015).

A large scale review of 9 clinical trials with 6286 patients with metastatic colorectal cancer was conducted by Sargent *et al.*.(Sargent *et al*., 2009). They found that patients with performance status 2 had significantly higher rates of grade ≥3 nausea and vomiting and 60 day all-cause mortality was 12% compared to 2.8% for patients who were performance status<2 ($p<0.0001$). Performance status 2 was prognostic for a lower progression free survival and response rate to chemotherapy.

Only one study was identified concerning the effect of co-morbidity on overall chemotherapy toxicity. LoConte *et al.* aimed to identify clinical and non-clinical factors that influence the occurrence of dose-limiting toxicity in phase I trials (LoConte *et al*., 2009). The authors reviewed 242 patients from 24 different phase I studies where the maximum tolerated dose was reached. In a bivariate analysis, mean age, household income, weight, body surface area, dose of drug, alkaline phosphatase, haemoglobin and lactate dehydrogenase were found to be significantly associated with dose limiting toxicity. Multivariate analysis showed that dose level and distance from the trial centre were significant predictors of dose limiting toxicity. Age and comorbidity did not predict the development of dose limiting toxicity. As the population in this study was so heterogeneous, given the small numbers involved, it was difficult to rely on the results. A prospective study to confirm the results was recommended.

An Australian study investigated the impact of obesity on toxicity in over 500 women treated with adjuvant chemotherapy for breast cancer (Carroll *et al*., 2014). It was concluded that obesity was not statistically related to risk of chemotherapy related admission or risk of febrile neutropenia. There was also no evidence of increased toxicity in obese women with either full or adjusted chemotherapy doses.

Lee *et al.* concluded that in women with advanced breast cancer, physical wellbeing and appetite are significant predictors of toxicity and also survival (Lee *et al*., 2010).

A retrospective study of patients with a GI malignancy found that malnourished patients received less chemotherapy due to toxicity related dose reductions (Klute *et al*., 2015). Multivariable logistic regression modelling was used to show that malnutrition was an independent predictor of receiving less than 80% of the standard dose of chemotherapy. This suggests that malnutrition has an effect on toxicity. It is probable that malnutrition is linked to performance status, but Klute *et al.* controlled for performance status and age in the regression model.

Wendrich *et al.* found that low skeletal muscle mass was an independent predictor of dose limiting toxicity in patients receiving chemotherapy for head and neck cancers (Wendrich *et al*., 2017). The study included 112 patients with locally advanced disease who were enrolled in clinical trials. It was not possible to extrapolate this data to a more generalised population as disease and other variables would be very different. Patients enrolled in clinical trials would have to fulfil entry criteria and many patients in a general population would have factors that exclude them from trials, that may affect toxicity, such as performance status, prior treatment or co-morbidity.

A study of 151 patients over 70 years of age receiving chemotherapy for a variety of diseases, found that performance status was predictive of toxicity and patients with a performance status of 2 or higher or co-morbidities, experienced more adverse events and were more likely to discontinue chemotherapy due to toxicity (Phaibulvatanapong *et al*., 2018).Higher performance status was also associated with a poorer quality of life. As this study only included patients over 70 years of age, it may not be possible to extrapolate the results to a population with a wider age range.

1.2.6.3 Genetic mutations

A Swiss study of early breast cancer patients concluded that the BRCA1/2

mutation status was a risk factor for febrile neutropenia after the first cycle of anthracycline based chemotherapy (Huszno *et al*., 2013). The analysis of 270 patients showed that although the risk of febrile neutropenia was increased in the BRCA1/2 positive group, this group seemed to not have an increased risk of other toxicities. This study may have suggested that genetic factors can have an effect on chemotherapy toxicity, however only a small population was used and only one genetic mutation in one disease is investigated. Shanley *et al.* partly concurred with these findings, in that they concluded that BRCA1/2 mutations are not associated with increased toxicity, however they also suggested that this applies to haematological toxicity and even stated that BRCA2 carriers appeared to have a lower incidence of neutropenia (Shanley *et al*., 2006). The two studies have slightly contradictory results, which could be as a result of different populations. Also the Shanley *et al.* study used patients treated much earlier than those in the Huszno *et al.* study, suggesting that treatments and supportive care available may have been very different.

1.2.7 Treatment Factors

Many different treatments are used in cancer treatment and are associated with different toxicities as described in trial data and listed in summaries of product characteristics. No literature was identified that explored the general relationship between treatment and toxicity.

1.2.7.1 Dose

Dose has long been known to affect the efficacy of chemotherapy, with most agents having a steep dose-response curve (Frei and Canellos, 1980). Indeed Frei described this as early as 1980, when far fewer treatments were available than now. Dose is less critical with certain drugs such as 5-fluorouracil but the review pointed out that in adjuvant therapy, dose-response is steep. There was also strong evidence that dose is strongly related to toxicity.

1.2.7.2 Intent of Treatment

The intent of anticancer treatment is crucial in the planning of effective of care of the cancer patient (Neal and Hoskin, 2009). The intent of treatment will be dictated by the potential outcomes, namely cure or palliation. The three main intentions of chemotherapy are:

- Adjuvant (in addition to another treatment modality with the aim of preventing spread or recurrence)
- Neoadjuvant (similar in intention to adjuvant chemotherapy, but given prior to another treatment modality, for example chemotherapy given prior to surgery. This can also have the intention of making a cancer operable or facilitating a different kind of surgery such as breast conserving surgery rather than mastectomy)
- Palliative (not aimed at cure, but at relief of symptoms but also prolonging life, without eradicating the cancer)

Different diseases are treated differently and with different intentions. The treatment intent and disease treated will dictate the type of chemotherapy used. It may often be necessary to choose treatments with fewer toxicities for treatment of palliative intent, when quality of life can become of greater importance.

Phaibulvatanpong *et al.* suggested that amongst other factors, patients receiving chemotherapy of palliative intent had a higher risk of toxicity, which resulted in those patient having a higher risk of discontinuing chemotherapy due to toxicity (Phaibulvatanapong *et al*., 2018). This study only involved patients over 70 years of age and so may not apply to a population with younger patients.

A meta-analysis of randomised controlled trials comparing low-dose to conventional dose chemotherapy in a number of different malignancies (Xie *et al*., 2017), suggested the opposite of Phaibulvatanpong *et al.,* in that low-dose chemotherapy can achieve similar overall survival rates and response rates to

conventional dose chemotherapy. Rates of certain toxicities were significantly less in the low-dose arms, which included mucositis (RR=0.31, 95%CI [0.19, 0.53], *P*<0.001), thrombocytopenia (RR=0.45, 95%CI [0.32, 0.64], *P*<0.0001), anaemia (RR=0.52, 95%CI [0.37, 0.73], *P*=0.001), febrile neutropenia (RR=0.73, 95%CI [0.58, 0.90], *P*=0.004). For diarrhoea (RR=1.78, 95%CI[0.35, 8.94], *P*=0.49), leucopenia (RR=0.50, 95%CI[0.21, 1.17], *P*=0.11), neutropenia (RR=0.91, 95%CI[0.52, 1.59], *P*=0.74), nausea/vomiting (RR=0.68, 95%CI[0.37, 1.24], *P*=0.21) and treatment-related death (RR=0.35, 95%CI[0.04, 3.31], *P*=0.36), there was no apparent differences between low and conventional dose chemotherapy. This evidence could have a significant impact on clinical practice as it suggested patients can achieve the same responses to chemotherapy with fewer side effects.

The 3 cancer diagnoses that received the most chemotherapy in the UK in 2014 were explored based on SACT data submitted by NHS trusts (Chemotherapy Intelligence Unit, 2014).

1.2.8 Breast Cancer

Data from 2013-15 showed that there were around 54,900 cases each year in the UK of invasive breast cancer, making it the first most common cancer in the UK (Cancer Research UK, 2015c). Since the early 1990's, incidence has increased in women by 25%. Early stage breast cancers accounted for 79-87% of new breast cancer diagnoses, with breast cancer having a favourable prognosis. More than 65% of patients with breast cancer will be alive in 20 years' time, with nearly 90% of patients surviving to five years. In 2014, 30,918 cycles of chemotherapy were given for breast cancer in the UK from trusts reporting SACT data (Chemotherapy Intelligence Unit, 2014).

Some interesting themes have emerged from the research around breast cancer. Hospital admission rates were reported but it is not known if these were

due to toxicity or other causes. The risk of death associated with specific treatments in specific groups of patients was also reported.

A single-centre Canadian study investigated all patients treated with curative chemotherapy for breast cancer (Pittman *et al*., 2015). Out of 149 patients, 88 (53%) required an emergency room visit and 19 (13%) required a hospital admission. The stage of breast cancer was found to be the only factor that was significantly associated with emergency room visits. Tumour size, lower number of chemotherapy cycles and adjuvant therapy were significantly associated with hospital admission. Of course this was a small study and may not be generalizable, however it did show some information regarding admission.

Petrelli *et al.* compared the relative toxicity of adjuvant anthracycline based chemotherapy to that of adjuvant taxane based chemotherapy in patients with breast cancer (Petrelli *et al*., 2012). This large meta-analysis included 15 randomised controlled trials with a combined patient population of 27039. The analysis reported an incidence of 4.5% of all-grade cardiotoxicity in breast cancer chemotherapy. The mean risk of death without breast cancer recurrence in all experimental arms was 0.94% versus 0.87% in control arms. The incidence of neurotoxicity was 5.4% in experimental groups versus 0.4% control arms. This study showed the relative incidences of several toxicities in breast cancer chemotherapy and was a good grounding for further research, however it did only include a limited number of toxicities.

A single centre US study reviewed 62 patients over 70 years old who received chemotherapy for breast cancer (Garg *et al*., 2009). A logistic regression model showed that increasing age was not associated with early termination of chemotherapy. However, increasing age, lower functional status and higher comorbidity in this patient group were associated with dose reduction and breaks in chemotherapy. Whilst this was a very small study, it did highlight

some of the potential consequences of toxicity and some factors which may influence it.

A prospective study of 143 patients in several centres who received 766 cycles of chemotherapy for breast cancer, were given diaries to record the frequency and severity of any nausea and vomiting (Booth *et al*., 2007). The following risk factors were found to be associated with nausea and vomiting; age younger than 40 years, nausea expectation, not eating before treatment and low alcohol use. Although this was a relatively small-scale study and the chemotherapy administered was not described in detail, it was useful in providing an overview of the prevalence of nausea and vomiting in breast cancer chemotherapy. It also concurred with the findings of studies looking at chemotherapy-induced nausea and vomiting, which are discussed later on in **Section 1.2.12**.

An American survey of 1945 women with early breast cancer treated with chemotherapy showed that 872 (45%) reported a toxicity rated as severe/very severe (Friese *et al*., 2017). Unscheduled clinic visits were required by 175 (9%) of patients for toxicity management and 97 (5%) visited a hospital or emergency department. Latina ethnicity, and receipt of chemotherapy and radiotherapy were predictors of toxicity. This study illustrated rates of patient reported toxicity and provided a good picture or the potential impact of toxicity.

FEC (Fluorouracil, Epirubicin, Cyclophosphamide) is a widely used regimen in breast cancer, so articles pertaining to the toxicity associated with FEC were searched. A German review of 1496 patients with breast cancer undergoing FEC chemotherapy, found that 639 (99.1%) of patients in the FEC arm reported a toxicity of some grade (Schönherr *et al*., 2012). Toxicities of grade 1 and 2 were seen in 83 (12.9%) of patients and of grade 3 and 4 in 1126 (86.2%) of patients. Toxicities were grouped as haematological and non-haematological. Severe (grade 3 or 4) non-haematological toxicities were rarely found, whereas grade 3 or 4 haematological toxicities were frequently

observed. Only 497 (77.1%) of FEC patients received the full course of chemotherapy, with many patients requiring dose reduction or discontinuation of therapy. The rate of early termination of chemotherapy was 8%. This trial gave some useful information around patients on adjuvant chemotherapy in breast cancer. The trial was very clinically focussed and did not report on any effects of that toxicity on the wider healthcare system or on the consequences of toxicity beyond those pertaining to the chemotherapy.

1.2.9 Lung Cancer

Lung cancer is the third commonest cancer seen in the UK with 46,700 new cases seen each year in 2013-15 (Cancer Research UK, 2015f). The second commonest cancer in the UK is prostate cancer (Cancer Research UK, 2014) however more cycles of chemotherapy were given in breast, lung and colorectal cancer, so prostate cancer was not included in the literature review (Chemotherapy Intelligence Unit, 2014). Overall, since the 1990s, lung cancer incidence has reduced by 8%. Lung cancer remains a difficult disease to cure with over 75% of patients being diagnosed at a late stage. Only 5% of people with lung cancer survive to 10 years, with 10% surviving 5 years or more. Smoking is the cause of 72% of lung cancers. In 2014, lung cancer was the 3rd commonest disease that chemotherapy was given for, with 18,216 cycles of chemotherapy being given in 2014 in the UK in trusts that reported SACT data (Chemotherapy Intelligence Unit, 2014).

Only one study of value was identified that looked specifically at toxicity in patients receiving chemotherapy for lung cancer. A large scale review was undertaken by Hardy *et al.* of patients with lung cancer treated with chemotherapy between 1991 to 2002 identified by an epidemiology database (Hardy *et al*., 2010). The study looked at 14 chemotherapy regimens and 50 toxicities, both long and short term. The most common short-term toxicities were anaemia, nausea and neutropenia with incidences between 9.2 and 60%. The most common long-term toxicities were anaemia, respiratory failure,

pulmonary fibrosis, dehydration, neutropenia, nausea and fever. Multivariate analysis for certain therapies showed that long term toxicity was more likely in women, minority populations and patients with fewer baseline comorbidities across disease stages. The study included over 70,000 patients. Although the study was relatively old, it still remained useful due to the very large population investigated.

1.2.10 Colorectal Cancer

Colorectal cancer is the fourth commonest cancer in the UK, seeing 41,700 new cases each year in 2013-15 (Cancer Research UK, 2015a). Since the 1990s, incidence of bowel cancer has increased by less than 5%. Almost 60% of patients diagnosed with colorectal cancer in the UK will live for 10 years or more, with a similar figure living for 5 years or more. Early stage bowel cancer accounts for 52-56% of diagnoses. Colorectal cancer was the second commonest cancer for which chemotherapy was given in 2014 in the UK from trusts reporting SACT data, with 20,884 cycles of chemotherapy being given (Chemotherapy Intelligence Unit, 2015).

A large Australian review article looked at various factors influencing survival and toxicity in chemotherapy for colorectal cancer (Chua *et al*., 2011). The group used pooled analyses and reviews of a large number of trials and meta-analyses to look at the various factors.

Age was the first thing to be investigated, data was reviewed from over 80 trials of patients treated with 5-fluorouracil, or oxaliplatin / irinotecan doublet regimens. Evidence was found in some studies to suggest an increased incidence of toxicity in the elderly population, especially in grade 3 or higher haematological toxicity. This would concur with the findings of other studies discussed above, outside of the colorectal setting. No difference in 60-day mortality was seen in different age groups. Less data was available to enable the authors to look at gender as a factor affecting toxicity. However numerous

large-scale trials have found severe mucositis to be more prevalent in female patients (22% versus 12% in males [p=0.0006]). Leucopenia is also seen more frequently in females. The group pooled data from large fluorouracil based randomized trials to look at performance status (PS). Several trials showed that patients with a higher performance status were more likely to experience non-haematological toxicity. The pooled analysis also showed that PS2 patients had a significantly greater 60-day, all-cause mortality (12% vs 2.8% [p<0.0001]). Studies involving patients being treated in the adjuvant setting were used to examine data on race and ethnicity. A large review of nearly 20,000 patients showed that African-Americans with colorectal cancer had a significantly higher mortality than other ethnic groups (HR 1.21-1.45 – confidence intervals not reported), although a smaller trial of 3380 patients did not demonstrate any difference in survival or toxicity rates. A pharmacogenomic study of 1412 patients treated for metastatic disease revealed few differences in survival but higher rates of grade 3 or higher adverse events in white patients.

Following common diseases, some common toxicities were explored in the literature.

1.2.11 Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) are two of the most common and troublesome side effects experienced by cancer patients (Janelsins *et al*., 2013).

Chemotherapy induced nausea and vomiting (CINV) appeared to be well studied with several international guidelines in existence. Nausea and vomiting are two distinct symptoms, closely related (Janelsins *et al*., 2013). Nausea can be defined as an unpleasant sensation experienced at the back of the throat and epigastrium, that can result in vomiting. Vomiting is the motor reflex resulting from forceful upward expulsion of the contents of the stomach. CINV

is classified as acute, delayed or anticipatory. Acute CINV occurs in the first 24 hours after chemotherapy is administered and lasts for a maximum of 5-6 hours. Delayed CINV occurs 24 hours after chemotherapy and can last for 5-7 days. Anticipatory CINV is a conditioned response that occurs prior to the administration of chemotherapy and is based on a patient's prior experience of chemotherapy, being triggered by olfactory, visual, psychological or auditory stimuli.

The CINV process is triggered by a number of physiological pathways after administration of the chemotherapeutic agent (Janelsins *et al*., 2013). The central nervous system plays an important role in CINV, receiving a variety of emetic stimuli and generating efferent signals to a number of tissues resulting in nausea and vomiting. Multiple emetic pathways exist and operate by a variety of mechanisms. The three main neurotransmitters are shown in **Table 2** along with the receptors with which they are associated.

Table 2. Neurotransmitters and Receptors

Neurotransmitter	**Receptor**
Serotonin (5HT)	5-hydroxytryptamine (5HT3)
Substance P	Neurokinin – 1 (NK1)
Dopamine	Dopamine receptors

Serotonin is the primary mediator of neural signals from the gut to the nucleus of the solitary tract (NTS) and activates 5HT3 receptors in the gut and NTS. Substance P transits signals from the vagus nerve to NK1 receptors in the chemoreceptor trigger zone in the area postrema on the floor of the fourth ventricle of the brain. Dopamine is likely to have anti-dyspeptic effects. Chemotherapy agents are toxic to the enterochromaffin cells lining the GI tract, causing formation of free radicals, which cause enterochromaffin cells to release excessive serotonin. The serotonin binds to 5HT3 receptors on vagal nerve afferents, relaying information to the brain which either initiates emesis directly or sensitizes the vagus nerve to other substances released from

enterochromaffin cells, or resulting from cell death, resulting in delayed CINV. Substance P is distributed throughout the central and peripheral nervous systems and is the preferred ligand for NK1 receptors, which are located in the gut, area postrema and NTS regions. Release is mediated by chemotherapy agents but substance P tends to bind largely to centrally located NK1 receptors, which signal vagal afferent nerves to the chemoreceptor trigger zone and the vomiting centre in the medulla oblongata. It is likely that centrally located signalling is most significant for CINV. It has been suggested that there is some cross talking between 5HT3 and NK1 receptor signalling pathways, in that once one receptor is activated by its ligand, it affects the cellular responses of another receptor system, resulting in a synergistic action, however this remains theoretical and has not yet been elucidated. There is emerging evidence that delayed CINV is largely associated with the activity of substance P. Other pathways that are less well understood are involved in CINV. The main anti-emetic drugs used in CINV work on the pathways described above. Their efficacy in treating CINV suggests that these are the primary mechanisms responsible for the reaction. For example the dopamine receptor antagonists domperidone and metoclopramide have a well-established role in the management of CINV, suggesting the role of dopamine in triggering CINV.

CINV is graded using the common terminology criteria for adverse events (CTCAE) as described by the US national cancer institute (National Cancer Institute, 2010). It is graded as in **Tables 3 and 4**.

Table 3. Nausea and CTCAE Grade

Nausea	
CTCAE grade	
1	Loss of appetite without alteration in eating habits
2	Oral intake decreased without significant weight loss, dehydration or malnutrition
3	Inadequate oral caloric or fluid intake: tube feeding, TPN or hospitalisation indicated
4	-
5	-

Table 4. Vomiting and CTCAE Grade

Vomiting	
CTCAE grade	
1	1 - 2 episodes (separated by 5 minutes) in 24 hrs
2	3 - 5 episodes (separated by 5 minutes) in 24 hrs
3	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalisation indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

It is known that the likelihood of nausea and vomiting is increased by the agents used, but also by a number of patient factors as described below.

The American Society of Clinical Oncology (ASCO) publish guidelines for the management of CINV (Hesketh *et al.,* 2017a). Anticancer agents are graded as to their emetogenicity and are graded as high, moderate, low and minimal with the risk of CINV being >90%, 30-90%, 10-30% and <10% respectively.

A longitudinal review of 200 patients receiving different chemotherapies for several cancers showed an incidence of nausea and/or vomiting in 123 (62%) of patients (Pirri *et al*., 2013). This was a relatively small study with a very heterogeneous population, however gave an indication of the incidence of nausea and vomiting in chemotherapy patients. Patients reporting nausea and/or vomiting reported a significantly impaired quality of life compared to those not experiencing nausea and vomiting. In a separate article, the same data is used to identify pre-treatment risk factors for nausea and vomiting (Pirri *et al*., 2011). In 77% of cases, the following risk factors predicted chemotherapy induced nausea and vomiting: female gender, premorbid/anticipatory vomiting, moderate to highly emetogenic chemotherapy, cancer resection and pre-treatment low role functioning.

Another, larger study identified variables which can be used to predict the risk of nausea and vomiting in chemotherapy patients, which included low social functioning, pre-chemotherapy nausea, female gender, highly emetogenic chemotherapy, low alcohol use and lack of maintenance antiemetics, which were all associated with a higher incidence of nausea and vomiting (Osoba *et al*., 1997). Risk factor analysis showed that the incidence of post chemotherapy nausea and vomiting increased from 20% in patients with no risk factors, to 76% in those with 4 or more risk factors.

The European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) stated in their antiemetic guidelines, that despite recent advances, nausea and vomiting remain a problem in chemotherapy patients (Roila *et al*., 2010). The guidelines classified chemotherapy agents into four groups for their emetogenicity and could be used to judge the likelihood of nausea or vomiting occurring based on drug factors alone. The guidelines are widely used in clinical practice. The guidelines also reviewed the evidence for antiemetic drugs and made recommendations as to which drugs to use when.

The American Society for Clinical Oncology (ASCO) guidelines followed a similar format to the MASCC guidelines and used literature reviews of randomized controlled trials to develop guidelines for use in clinical practice (Basch *et al*., 2011). The MASCC guidelines agreed with most of the drug classifications (Roila *et al*., 2010). As these guidelines were so extensive, included large numbers of randomized controlled trials and were internationally utilised; it could have been supposed that it was most likely to see nausea and vomiting in patients receiving the highly emetogenic drugs. However, these guidelines did not consider patient influences as part of these classifications.

A 2016 secondary review of a trial looked at the use of gabapentin in the prevention of CINV in 413 patients receiving highly emetogenic chemotherapy (Kottschade *et al*., 2016). The authors found that 145 (35%) of patients reported nausea and 78 (19%) at least one emetic episode. CINV on day 1 of cisplatin therapy and history of motion sickness significantly predicted delayed CINV. Age, combination of highly and moderately emetogenic chemotherapy and being treated for breast cancer, predicted CINV on day 1. These results concurred with other studies suggesting these factors as predictive of CINV.

Escobar *et al.* looked at the incidence of CINV in 240 patients receiving moderately emetogenic chemotherapy (Escobar *et al*., 2015). Vomiting occurred within 5 days of chemotherapy in 50 (20.8%) of patients and nausea in 100 (42%). This suggested that CINV was problematic in this population of patients.

A small study aimed to investigate the impact of CINV on patients' quality of life (Lindley *et al*., 1992). Patient diaries, a functional living index – cancer tool, a functional living index – emesis tool and an item checklist for cost implications were used prior to and after chemotherapy for a variety of indications in 122 patients. CINV was reported by 68 (56%) of patients. Statistically significant reductions in quality of life scores were seen in patients who experienced CINV but not in those who did not. Patients who experienced CINV found that their

ability to complete household tasks, enjoy meals, spend time with family and friends and to maintain daily function and recreation was impaired. Although this was a small study, it highlighted the potential consequences of CINV and confirms that it was generally considered to be a negative symptom.

A German study of 208 chemotherapy cycles of emetogenic chemotherapy for a number of different cancers found that 68 (32.8%) of patients experienced acute CINV (Ihbe-Heffinger *et al*., 2004). Rates of delayed CINV were much higher at 60.7% (126 patients). Healthcare resources were utilised by 68 (32.6%) of patients due to CINV. Only one patient required hospitalisation and only 3 patients lost work days due to CINV. High costs for management of CINV were seen in patients who received a cisplatin containing regimen, those who had a worse experience of CINV and those who experienced delayed CINV. Although this was a small study it gave an indication as to the resource implications for the health care system of CINV, confirming that it was a significant toxicity and that there was value in researching the risk factors associated with it. The study only took place in one country with a single health system, so may not be generalisable to other health systems internationally.

A large scale review article of the pathophysiology and treatment of CINV suggested that younger age and female gender were predictors of toxicity (Hesketh, 2008), although this was based on evidence from trials looking at cisplatin based chemotherapy, so may not have been applicable to all treatments. Hesketh also suggested that emetogenicity of treatment and dose would affect the risk of CINV. Patients who have a high alcohol consumption were less likely to experience CINV.

1.2.12 Diarrhoea

Mucositis is a common side effect of chemotherapy. When it affects the lower gastrointestinal tract it can result in diarrhoea. The mechanisms of damage to the gut by chemotherapy are not fully understood (Gibson and Keefe, 2006). It

is thought that the effects of chemotherapy on the different parts of the gastrointestinal (GI) epithelium are via different mechanisms, as the colorectal epithelium is mainly columnar in structure, whereas higher up the GI tract the epithelium consists of a renewing stratified squamous mucosa. Diarrhoea can be defined as an increased frequency and decreased consistency of bowel motions, which may be associated with blood, pain and mucous.

Several different types of diarrhoea can be caused by chemotherapy (Gibson and Keefe, 2006):

- Secretory – occurs when absorptive capacity of the mucosa is exceeded by secretory activity, increasing luminal contents. It is associated with increased secretion of electrolytes
- Osmotic – occurs when there is a higher concentration of osmotically active or non-absorbable solutes in the lumen
- Malabsorption – can result from alterations to the microflora, or damage to the villi of the GI tract. Rebound crypt hyperplasia can occur, where immature crypt cells develop in the colon, which produce immature enzymes, which can reduce water absorption. In the crypt wall, water absorption follows chloride ions. When the crypt cells are damaged, chloride is not absorbed and so water remains in the lumen, resulting in diarrhoea.
- Exudative – can increase mucus secretions
- Dysmotility – occurs when gut motility is increased. If transit time is increased, less water can be absorbed, resulting in diarrhoea
- Infectious – occurs when a pathogen is present and can be secretory or osmotic
- Inflammatory – can occur when medications result in inflammation of the GI tract
- Steatorrhoea – can result from deranged secretions of bile salts

Precise mechanisms of diarrhoea induced by chemotherapy have not been fully explored, although there was limited evidence that elucidated this. It has

been theorised that diarrhoea is caused by a combination of mechanical and biochemical changes caused by chemotherapy, resulting as a direct toxicity of the chemotherapy on colonic crypt cells (Gibson and Keefe, 2006). It is also thought that the villi in the small intestine may be unable to absorb fluids correctly and other changes may be associated with intestinal inflammation, which leads to secretion of mucosal and submucosal factors. It has been suggested that chemotherapy destroys brush border enzymes and causes more gut wall secretions to occur (G. Richardson and Dobish, 2016). Another possible mechanism is that chemotherapy alters the bacterial microflora and results in bacterial overgrowth, with a resultant increase in enterotoxins, leading to a direct secretory effect on the intestinal mucosa.

Targeted anticancer agents were also associated with diarrhoea (Stein *et al*., 2010). Epidermal growth factor receptor (EGFR) targeted agents have a rate of grade 3-4 diarrhoea of less than 10%, however EGFR targeted monoclonal antibodies (MABs) can have higher rates, up to 60% of all grade diarrhoea. Multi-targeted tyrosine kinase inhibitors (TKIs) can have a rate of all-grade diarrhoea of 30-50%. mTOR inhibitors cause diarrhoea in up to 40% of patients. The mechanisms by which diarrhoea is induced by these newer agents are not yet fully understood. One potential mechanism is an alteration of intestinal motility (Stein *et al*., 2010).

Diarrhoea is commonly graded using the CTCAE system, as in **Table 5** (National Cancer Institute, 2010).

Table 5. Diarrhoea and CTCAE Grading

Diarrhoea	
CTCAE grade	
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of >=7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

Irinotecan is a chemotherapeutic agent, which is associated with high rates of diarrhoea (60-80% of patients) (Gibson and Keefe, 2006). Two distinct types of diarrhoea are seen with irinotecan, an early secretory diarrhoea, which is a manifestation of a cholinergic reaction to the irinotecan, and a delayed diarrhoea. A study of jejunal and colonic histology following irinotecan administration suggests that it increases apoptosis in crypts of the GI tract and causes villous atrophy and crypt hypoplasia resulting in increased mucus secretion and changes in absorption rates (Gibson *et al*., 2003). Irinotecan is metabolised to SN-38, the active metabolite, by carboxylesterase. SN-38 is further metabolised to SN-38 glucuronide (SN-38G). When SN-38G is secreted into bile, it has to pass through the intestine, where bacteria convert some of it back to SN-38, by bacterial β-gluronidase, where it can cause further gut-toxicity.

5-fluourouracil is another common chemotherapeutic agent that is commonly associated with diarrhoea (Gibson and Keefe, 2006). Few animal models have

been conducted to explore the mechanism by which 5-fluorouracil causes diarrhoea, so it is not possible to elucidate this at present.

Data on rates of diarrhoea was difficult to find outside of trials investigating individual agents or regimens. It is thought that diarrhoea can occur in 50-80% of patients depending on the regimen used (Stein *et al*., 2010). A 2011 meta-analysis reviewed randomized controlled trials comparing targeted agents to standard FDA approved chemotherapy regimens for all cancers (Elting *et al*., 2013). The incidence of diarrhoea was higher in nearly all trials with the targeted agents with relative risks ranging from 1.5 to 4.5. As targeted therapies are now widely used, this study highlighted the potential burden of diarrhoea as a toxicity.

Andreyev *et al.*, conducted a large review of the literature around chemotherapy induced diarrhoea and concluded that there was a lack of randomized controlled trials (Andreyev *et al*., 2014). The authors developed UK multi-disciplinary guidelines for the management of diarrhoea based on the evidence reviewed.

A review of 18 trials of anti-epidermal growth factor receptor monoclonal antibodies in patients with colorectal cancer found that these patients had a relative risk of diarrhoea of 1.66 (95% CI [1.52-1.8]) (Miroddi *et al*., 2015). The relative risk of mucositis was 3.44 (95% CI [2.66-4.44]). Although this study focused on a single tumour site and class of drugs, it demonstrated the risk of diarrhoea in this patient group.

1.2.13 Fatigue

The national cancer institute defines fatigue as:

“A condition marked by extreme tiredness and inability to function due to lack of energy. Fatigue may be acute or chronic.”

(National Cancer Institute, 2018)

Fatigue is known to be a very common symptom in patients with advanced cancer (Barnes and Bruera, 2002). The aetiology of fatigue is unclear but it has been shown to have physical and cognitive effects. Fatigue is a subjective sensation and so assessment can be difficult. Many factors are thought to contribute to fatigue including cancer, cancer treatment, cancer or treatment complications, medication and other physical or psychosocial conditions. There are many fatigue assessment tools available that can help to identify and manage fatigue. Fatigue rates of up to 99% have been reported in some trials, but many of these did not focus on chemotherapy patients, but cancer patients as a population. Management of fatigue can involve specific or symptomatic interventions. Specific interventions include:

- correcting anaemia or metabolic abnormalities
- managing pain
- managing insomnia
- managing depression and anxiety

Symptomatic measures include:

- Education
- Counselling
- Pharmacologic treatment – including corticosteroids, progestational agents and psychostimulants
- Non-pharmacological interventions – including psychosocial interventions and physical activity

(Barnes and Bruera, 2002)

Fatigue can be graded in accordance with CTCAE criteria as in **Table 6.**

Table 6. Fatigue and CTCAE Grading

Fatigue	
CTCAE Grade	Description
1	Fatigue relieved by rest
2	Fatigue not relieved by rest limiting instrumental ADL
3	Fatigue not relieved by rest limiting self-care ADL
4	-
5	-

(National Cancer Institute, 2010)

This is a very subjective way of measuring fatigue as fatigue is a personal phenomenon that may be felt differently by different patients. As such, a standardised means of measuring fatigue has not been reached by consensus (Hauser *et al*., 2008).

There did not appear to be one clear pathophysiology of fatigue in cancer and many studies have focussed on factors that contribute to it rather than the mechanism of fatigue development (Wang, 2008). Various hypotheses around the pathophysiology of fatigue have been proposed. The central governor model proposed that the subconscious brain regulates power output by modulating motor unit recruitment to preserve whole body homeostasis, in order to prevent catastrophic physiological failure (Weir *et al*., 2006). Although this model suggested a purpose and mechanism for fatigue, it had little evidence to back it up. Chaudhuri and Behan implicated metabolic and structural lesions that disrupt the usual process of activation in pathways interconnecting the basal ganglia, thalamus and limbic system and higher cortical centre in the pathophysiological process of “central” fatigue (Chaudhuri and Behan, 2004). Wang suggested that cancer related fatigue fits well in to Chaudhuri and Behan’s model, in which fatigue was a complex emotion

affected by motivation and drive, fear and anger and memory of prior activity (Wang, 2008).

Ryan *et al.* conducted a review of many studies investigating potential mechanisms to explain the pathophysiology of cancer related fatigue. The review stated that fatigue mechanisms have been proposed in various conditions and often these were extrapolated to cancer (Ryan *et al*., 2007). Another proposed mechanism of fatigue was serotonin (5-HT) dysregulation. It was suggested that cancer or cancer treatment causes an increase in serotonin in the brain and /or upregulation of 5-HT receptors, which results in reduced somatomotor drive, modified hypothalamic-pituitary-adrenal axis (HPA) function and a sensation of reduced capacity to perform physical work. The effect on dysregulation on the various functions of serotonin can also explain fatigue, including appetite control, sleep, memory, learning, temperature regulation, mood, behaviour, cardiovascular function, muscle contraction, endocrine regulation and depression. Serotonin is also implicated in exercise-induced fatigue in chronic fatigue syndrome. Ryan *et al.* went on to link the serotonin theory to cancer related fatigue. There was evidence that proinflammatory cytokines such as TNF-α seen in cancer, can increase 5-HT metabolism, with existence of a feedback loop between TNF-α, that results in increased 5-HT being released into the synapse. It is also suggested that TNF-α can increase 5-HT transporter function, resulting in clearance of 5-HT from the synapse. It is also thought that TNF-α synthesis can be reduced by 5-HT. Pathologic conditions or treatment could dysregulate this feedback loop.

Ryan *et al.* cited HPA axis dysfunction as another possible mechanism to explain cancer related fatigue. Low levels of cortisol have been observed in patients with chronic fatigue syndrome, and it is suggested that cancer or cancer treatment could alter the function of the HPA axis, which causes endocrine changes that could be responsible for fatigue. The HPA axis regulates cortisol levels and cortisol is known to have a number of effects included blood pressure regulation, cardiovascular function, carbohydrate metabolism and immune function. Although the link between the HPA axis and

cancer related fatigue remains unclear, some evidence did indicate that HPA axis function is altered in cancer related fatigue, with one study finding lower serum cortisol levels in women with breast cancer who reported fatigue compared to those who did not report fatigue (Bower *et al*., 2002). This study only looked at breast cancer survivors and was post chemotherapy not during treatment.

A further mechanism to explain fatigue was circadian rhythm disruption (Ryan *et al*., 2007). Several studies have demonstrated alterations to circadian rhythm in cancer. These can include changes in endocrine rhythms such as cortisol, metabolic process such as circulating protein levels, the immune system such as levels of circulating cytokines and rest-activity patterns. These studies have shown that in patients with advanced cancer, greater rhythm alterations are demonstrated compared to healthy individuals.

Ryan *et al.* also argued that muscle metabolism and ATP disruption could explain cancer related fatigue. Various studies have confirmed that there is a negative correlation between cancer related fatigue and physical performance. A possible explanation was that cancer or its treatment leads to a defect in the mechanism for regenerating ATP in skeletal muscle, which compromises the ability to perform mechanical tasks.

Vagal afferent nerve activation was also suggested, by Ryan *et al.*, as a possible mechanism of cancer related fatigue. The hypothesis proposed that cancer or its treatment causes a peripheral release of neuroactive agents that activate vagal afferent nerves, leading to suppression of somatic muscle activity.

Ryan *et al.* also suggested that cytokine dysregulation could play a role in cancer related fatigue. Various studies have found that administration of proinflammatory cytokines like TNFα, can induce fatigue. TNF has been

associated with alterations in neurotransmission, causing behavioural changes such as lethargy and anorexia. Cancer and cancer treatments are associated with increases in plasma levels of cytokines and have been correlated with fatigue in cancer patients.

Fatigue often presents in cancer patients as a syndrome of several symptoms (Ryan *et al*., 2007). It can occur concurrently with conditions that are likely to contribute to fatigue, including anaemia, cachexia, depression and sleep disorders. As much chemotherapy is myelosuppressive, anaemia is a common side effect (Neal and Hoskin, 2009). Cachexia is thought to affect up to 50% of all cancer patients and the mechanism is not clearly understood (Ryan *et al*., 2007). Depression is seen commonly in cancer patients and has been shown in several studies to be associated with fatigue. Sleep disorders can also be seen frequently amongst cancer patients and there are a variety of mechanisms by which cancer or cancer treatment can disturb sleep.

A 2008 review of 531 patients who underwent chemotherapy for a number of different cancers in the advanced setting, suggested that fatigue was the top ranked symptom that impacted on patients' lives (Butt *et al*., 2008). Patient fatigue ratings were strongly associated with malaise, difficulties with activities of daily living, pain and quality of life.

A Cochrane review of studies investigating the use of exercise in the management of fatigue, suggested that exercise is effective in reducing fatigue during or post adjuvant cancer therapy in breast and prostate cancer (Cramp and Bryon-Daniel, 2012). This was a large review including 4068 patients and suggests a useful non-pharmacological management of fatigue. It did however leave the question of effective management of fatigue in patients receiving palliative chemotherapy, unanswered.

Poort *et al.* suggested that patients with advanced cancer receiving palliative chemotherapy, are likely to be ill for a long period of time, meaning that fatigue can have a prolonged and profound effect on quality of life (Poort *et al*., 2017). This made it an area of interest for research, as effective prediction and management may result in improved quality of life.

Hauser *et al*. suggested that cancer related fatigue is a frequently reported symptom that is affected by the diagnostic criteria and stage of disease (Hauser *et al*., 2008). Fatigue has many potential causes and Hauser *et al.* listed all types of cancer treatment as being associated with fatigue. One hundred and seventy one advanced cancer patients referred to the palliative medicine service in a single centre were surveyed, and 100 patients completed the survey. The mean age of the population was 65 years and there was a reasonable distribution of patients with different diagnoses. Although chemotherapy could not be associated with fatigue, Hauser *et al.* found that fatigue was associated with a higher performance status and worse physical function. Interference with work, enjoyment of life, mood, sleep and walking were also attributed to cancer related fatigue. Fatigue was greater in those with brain metastases and lower in those who had received prior radiotherapy treatment. Although this study was not specific to chemotherapy, it provided a useful overview of cancer related fatigue in a fairly heterogeneous population.

A Dutch review of 22 studies looking at fatigue in cancer patients on treatment found that the rate of fatigue reporting tended to differ with the different tools used (Servaes *et al*., 2008). One study reviewed reported that 60 (61%) of a mixed sample of cancer patients reported clinical fatigue during chemotherapy or radiotherapy (Graydon *et al*., 1995). In two studies where patient diaries were used, fatigue prevalence rates of 99% (76 patients) and 90% (116 patients) were reported at some point in chemotherapy (A. Richardson and Ream, 1996; Blesch *et al*., 1991). Six studies were found that compared cancer patients with healthy control patients and cancer patients reported more frequent and more severe fatigue than the control group (Stone, Richards, *et al*., 2000; Stone, Hardy, *et al*., 2000; Jacobsen *et al*., 1999; Hann *et al*., 1999;

Glaus, 1993). Ten studies were reviewed that compared pre and post - treatment fatigue scores and patients were significantly more fatigue mid- or post-treatment, although this included patients on other treatment modalities as well as chemotherapy (Stone, Richards, *et al*., 2000; Smets *et al*., 1998; Irvine *et al*., 1998; Irvine *et al*., 1994; Ahsberg and Furst, 1991; Hann *et al*., 1999; Dean *et al*., 1995; Monga *et al*., 1999; Jacobsen *et al*., 1999). Most studies failed to find relationships between fatigue and disease-related variables. No conclusions around fatigue and treatment-related factors were drawn as the authors stated that these relationships have rarely been investigated. In 10 out of 12 studies investigating interventions around fatigue, positive effects were reported on fatigue immediately after the intervention (Cimprich, 1993; Mock *et al*., 1997; Dimeo *et al*., 1999; A. Schwartz, 2000; Oyama *et al*., 2000; Spiegel *et al*., 1981; Worden and Weisman, 1984; Forrester *et al*., 1985; Houts *et al*., 1986; Fawzy, 1995; Cousins *et al*., 1990; Gaston-Johansson *et al*., 2000). The interventions included individual counselling, a walking or exercise programme or group meetings. In 3 studies the positive effect of the intervention was still apparent 3 to 6 months later (Worden and Weisman, 1984; Fawzy, 1995). This review provided very useful data on fatigue and highlighted that it is a troublesome side effect of chemotherapy, but can be successfully managed.

Much of the literature around fatigue appeared to be in patients with advanced cancer and little literature was found that looked at patients treated in the curative setting with adjuvant or neoadjuvant chemotherapy. This left an area of interest for this research.

1.3 Conclusions from the literature

Much literature has been identified around chemotherapy toxicity. Generalised data on chemotherapy toxicity did not seem to be available and it was difficult to ascertain an overall incidence or prevalence across all diseases and treatments. Data pertaining to the economic effects of chemotherapy toxicity was sparse and data on the risk of hospital admission due to toxicity could not be identified. Various studies highlighted the potential consequences of toxicity, which included morbidity, treatment adjustment and death. Indeed, toxicity has been shown to be a prognostic indicator in certain circumstances.

Various risk prediction tools have been developed for toxicity and some pertained to different sub-populations. All were validated or tested to different extents. Multiple studies were found that looked at age as a factor in toxicity. A number of other patient factors were investigated and found to influence toxicity to different extents. The top three most common cancers were explored and literature found that looked at chemotherapy toxicity in these populations. Frequently occurring toxicities were also researched and literature found that explained the pathophysiology of these toxicities and their occurrence with chemotherapy.

2.0 Aims and Objectives

The main aim of the research was to identify what factors influence the likelihood of patients experiencing acute chemotherapy toxicity and the likelihood of that toxicity leading to hospitalisation. It was hoped that this research would be able to give treating clinicians and institutions an idea of the impact of toxicity on both patients and the wider healthcare system.

The aims of the research were divided into the following objectives:

- To establish the overall incidence of toxicity
- To establish the incidence of hospitalisation due to toxicity
- To establish how the occurrence / severity of toxicity, the risk of hospitalisation is affected by the following
    - Age
    - Performance status
    - Treatment intent
    - Disease being treated
    - Treatment given (when grouped in different ways)

The research aimed to perform an analysis of the economic impact of toxicity and its consequences. This required the overall incidence of chemotherapy toxicity across all tumour sites to be elucidated. Once done, it was compared to the overall incidence of hospital admission. Toxicity is generally felt to be a negative phenomenon for the patient, although some literature, described above, suggested a correlation between toxicity and improved outcomes of treatment. However there was also much literature described above to suggest that toxicity can be detrimental and as such, the ability to predict and thus reduce that toxicity is seen as a positive action. Once factors affecting toxicity had been identified, it was then necessary to consider what actions can be taken to minimise the risk. This was not within the remit of this research.

2.1 Hypotheses

From the literature, it was possible to make various predictions about the outcome measures. Although no literature was found that would allow direct comparisons to this study, data was found that allowed comparisons to be made.

It was anticipated that the population would be heterogeneous, with a wide age range, as NUH is a large teaching centre, which treats all type of cancers across the East Midlands region of the UK (Nottingham University Hospitals 2014). It was thought likely that most patients would be performance status 0 to 2 as chemotherapy is less frequently given to patients of performance status >2 as discussed in the NCEPOD report, due to the possibility that risk could outweigh benefit (Mort *et al*., 2008). Data from Cancer Research UK and the national SACT data submissions, suggested that breast, colorectal and lung were likely to be the most common diseases (Cancer Research UK, 2014). Palliative intent was expected to account for a large proportion of the treatments given, due to the regimens available at NUH and a significantly larger number of palliative regimens being available and used. This data can be found internally on the NUH Chemocare® system (CIS, 2014). Due to the number of different regimens available at NUH, it was likely that a large number of treatments would appear in the data and that methods of grouping would be required in order to analyse the data in a meaningful way. It was anticipated that treatments could be grouped according to cytotoxicity, emetogenicity, the number of drugs used in the regimen, the class of drugs and the commissioning status of the drug. These were discussed in detail in the methodology.

The literature did not identify any data from an entire chemotherapy population that reported an overall incidence of toxicity. Jenner *et al.* found a rate of 29% grade 3 or 4 toxicity in a population limited to a small number of disease types (Jenner *et al*., 2010). This included acute and delayed toxicities, however it was felt that the toxicity rate seen in this research was likely to be higher than this

as it would include grade 1 and 2 toxicities as well as grade 3 and 4. It was hypothesised that nausea and vomiting would be reported frequently and may be the highest reported toxicities seen based on the rates of CINV quoted by Pirri *et al.*, Osoba *et al.*, Kottschade *et al.*, Escobar *et al.*, Lindley *et al.* and Ihbe-Heffinger *et al.* (Pirri *et al*., 2013), (Osoba *et al*., 1997), (Kottschade *et al*., 2016), (Escobar *et al*., 2015), (Lindley *et al*., 1992), (Ihbe-Heffinger *et al*., 2013). The data from Stein *et al.* and Mirrodi *et al.* suggested that diarrhoea was likely to be frequently reported and may have been one of the most frequent toxicities seen (Stein *et al*., 2010), (Miroddi *et al*., 2015). The data presented by Barnes and Servaes *et al.* would suggest that the incidence of fatigue would be very high and fatigue may have been the most frequently reported toxicity (Barnes and Bruera, 2002), (Servaes *et al*., 2008).

Age was expected to have an effect on the occurrence of toxicity, but this effect was unclear as the data found in the literature was contradictory. As such, a relationship with age and toxicity was expected but the direction of that relationship was unclear, however given the physiological changes seen in ageing patients, it was anticipated that age would increase the likelihood of toxicity (Balducci and Extermann, 2000).

Different cancer types are associated with different symptoms (Neal and Hoskin, 2009), so it was hypothesised that disease would have an effect on toxicity, however it was unclear what that effect would be as no data was found in the literature which explored this.

Sargent *et al.* and Phaibulvatanapong *et al.* both found that toxicity increased with performance status (Sargent *et al*., 2009; Phaibulvatanapong *et al*., 2018). These studies were not in populations with the same characteristics as was planned in this study, and looked at delayed as well as acute toxicity, however it was anticipated that higher rates of toxicity would be seen in the higher performance status patients.

Much of the literature cited treatment characteristics as predictors of toxicity. It is known that different treatments are associated with differing rates of toxicities. However, this research aimed to group the treatments and little literature was found that provided a basis for any hypotheses, so the hypotheses around treatment were more difficult to establish, but the following hypotheses were made:

- Treatment intent was felt likely to influence the occurrence of toxicity, as if the goal of treatment is cure, higher doses or more intensive chemotherapy may be used (Neal and Hoskin, 2009).
- It was theorised that cytotoxic treatment would result in higher rates of toxicity than non-cytotoxic and those regimens with a cytotoxic and non-cytotoxic agent would cause the highest rates of toxicity due to the additive effect of the agents. It is well-established that cytotoxic chemotherapy is associated with toxicity, both acute and delayed (Neal and Hoskin, 2009). It is also known that the targeted agents, which make up the majority of the non-cytotoxic treatment group, are associated with toxicity, but it is suspected that this is to a lesser extent than cytotoxic chemotherapy.
- It was hypothesised that the higher the number of drugs, the higher the rate of toxicity, as multiple agents could have an additive effect.
- No hypothesis was made about commissioning status of drugs as this had no scientific basis or background in the literature, but is of interest to the health economy.
- No hypothesis could be made about the effect of drug class on toxicity, although it was suspected that different classes of drug would be associated with different rates of toxicity, due to the side effect profiles of the drug class.
- It was hypothesised that toxicity would be higher, the higher the emetogenic potential of a regimen. Different agents are known to be associated with different rates of toxicity (Hesketh, *et al*., 2017a). If CINV is higher in highly emetogenic treatments, then this would increase the overall incidence of toxicity.

It was more difficult to find data on grade of toxicity outside of clinical trials of individual drugs or regimens. As such, making hypotheses around the grade of toxicity was more difficult. It was expected that more low grade (1 or 2) toxicities would be seen than higher grade (3 or 4) as this study only looked at acute toxicity and more severe toxicity may take longer to develop, although acute emesis is a well-documented side effect of chemotherapy, which may have meant that higher grades of nausea or vomiting would be seen (Hesketh, 2008). It was considered that as the rate of toxicity increased, so would the severity, although no data was found to support this theory. Higher grades of toxicity were expected in patients with a higher performance status, as these patients would have a lower functional state and so a toxicity in addition to symptoms of a condition or co-morbidity may have been more severe. The same was suspected of treatments containing more than one drug as it was anticipated that the toxicities of individual agents in these regimens could have an additive effect.

Hospital admission was an expected consequence of chemotherapy toxicity in some cases. Admission within 30 days of chemotherapy seemed an appropriate measure due to the NCEPOD report findings and recommendations (Mort *et al*., 2008) and also as admission within 30 days of chemotherapy had been the main focus of the CATT team. No data was found on admission rates in patients on chemotherapy, so no basis was available for predictions to be made. It was suspected that as more toxicity was seen, higher rates of admission would be seen. By definition, a grade 3 toxicity is severe or medically significant and hospitalisation or prolongation of hospitalisation is indicated (National Cancer Institute, 2010). A grade 4 toxicity is defined as life-threatening. Predicting length of stay was more difficult as there appeared to be so many factors that can contribute to this (Clarke, 1996) and there was a lack of literature around length of stay in admission due to chemotherapy toxicity.

In terms of the sub-group analyses, it was anticipated that these sub-populations would follow a similar pattern to the whole study population, as there was no data to suggest otherwise. It was acknowledged that there may

have been interactions between variables, for example the proportions of patients in the treatment intent groups was likely to differ as would treatment used. It was anticipated that more toxicity would be seen in the breast cancer patients as more treatment of adjuvant or neoadjuvant intent was likely to be used (Cancer Research UK, 2015c). Lung cancer patients were expected to have a higher performance status and thus report more toxicity (Cancer Research UK, 2015f).

The secondary outcome measures were expected to be fatigue, nausea and vomiting as described above. Diarrhoea was possibly expected to be one of the top 3 reported toxicities. Nausea and vomiting were expected to follow the same pattern and occur at similar rates as they are closely related symptoms (Hesketh, 2008). Given the data from Kottschade *et al.* and Hesketh, younger patients were expected to report more CINV (Kottschade *et al*., 2016; Hesketh, 2008). Incidence was expected to be higher in patients with poorer performance status as Pirri *et al.* suggested that low role functioning is predictive of CINV (Pirri *et al*., 2013). It was also expected that incidence would be higher in the adjuvant and neoadjuvant treatments due to the higher intensity. Treatments with more than one drug were expected to have higher rates of nausea and vomiting due to the additive effect and different drugs classes were expected to have higher rates according to side effect profiles. The higher emetogenic agents were expected to result in more nausea and vomiting due to the evidence base used in the guidelines (Basch *et al.,* 2011). Nausea and vomiting is a side effect associated with cytotoxic chemotherapy (Neal and Hoskin, 2009) and as such it was anticipated that higher rates would be seen with these treatments.

It was anticipated that fatigue or diarrhoea would be the third most commonly occurring toxicity. It was felt that either would be affected by the same predictors as toxicity and would follow similar patterns.

3.0 Methodology

3.1 Data Collection

The CATT telephone assessment service at NUH provided a unique opportunity to study acute chemotherapy toxicity. One of the main drivers for establishing the service was that the within 30 days of the first cycle of chemotherapy, the risk of admission due to toxicity was felt to be highest, based on clinical experience. As such the CATT team was established along with the telephone call back service which involved setting up an automated report from Chemocare®, the electronic chemotherapy prescribing system in use at NUH, which identified all oncology patients who had received a first cycle of chemotherapy in the previous 24 hours. As per the standard operating procedure in appendix 1, a nurse from the CATT team would place a telephone call to the patient in the 24 hours after chemotherapy and perform a thorough toxicity analysis as detailed in appendix 1. The fields shown in appendix 2 were based on the UKONS chemotherapy toxicity assessment tool as this is something that the nurses were used to working with within NUH (Jones *et al*., 2010).

A database was created in an Excel® (Microsoft, 2011) spread sheet, which was completed by the nurse undertaking the first telephone call. The spread sheet was stored in the acute oncology shared drive on NUH computers that could only by accessed by members of the acute oncology team. Prior to undertaking the call back service, all nurses within the CATT team received a short training session from a pharmacist, setting out the expectations of the service and the data that required collecting. It was intended to be as user friendly as possible and was set up with drop down menus for each toxicity along with descriptions of each grade of toxicity to allow for ease of data collection. Different tumour sites were set up with individual spread sheets. Patient demographics were recorded and the tab for the appropriate chemotherapy regimen was selected.

ECOG performance status was collected from the electronic prescribing system used to generate all chemotherapy prescriptions. This is a mandatory field and must be completed by the prescriber prior to prescribing any chemotherapy.

Treatment intent was evident from the Chemocare® record for each patient, as the care episode requires the prescriber to enter an intention of treatment. The treatment given was also obvious from Chemocare®.

Periodically, admission data was reviewed from the trust patient administration system. The patient details and reason for admission of all oncology patients at NUH was received. It was then necessary to exclude patients admitted for a reason other than chemotherapy toxicity. This was then amalgamated with the toxicity database to show which patients have had an admission following chemotherapy and for what reason.

3.2 Data Analysis

Once the call back service had been in operation for one year, the data for January to December 2015 was analysed. For the purposes of investigation patient identifiers were removed from the Excel® spread sheet and data was reviewed to ensure correct recording. It was then converted into alphanumeric data that would be suitable for SPSS® (IBM, 2013). The data was transferred into the SPSS® software for analysis and use in the research.

Much of the research was based on exploratory analysis. The initial data analysis plan was used and other areas explored according to findings.

The first step was to review and describe the study population using descriptive statistics around age, disease type, intent of treatment, types of treatment given and performance status. This established the context of the study.

Age was determined from the date of birth and date of chemotherapy entered into the spread sheet, using the Excel® tool. Age was then grouped in the following manner in order to facilitate analysis:

- <21 years
- 21-40
- 41-50
- 51-60
- 61-70
- 71-80
- >80 years

Even intervals were chosen in addition to the upper and lower extremes of the ages. Age was treated as continuous data in some analyses but also grouped and treated as ordinal data as done by Hurria *et al*. (Hurria *et al*., 2011).

It was anticipated that a heterogeneous population would be studied and that there would be a wide range of cancer diagnoses treated. In order to aid data analysis, the diseases were grouped according to the multidisciplinary team tumour sites used in clinical practice at NUH. These were:

- Central Nervous System (CNS)
- Breast
- Lower Gastrointestinal (GI)
- Gynaecology
- Cancer of Unknown Primary (CUP)
- Head and Neck
- Upper GI
- Lung
- Skin
- Sarcoma
- Urology

For drug treatment used, it was anticipated that there would be a large number of possible regimens used. It was therefore decided to group the treatments according to several different factors that related to clinical use and to treat these as separate variables. Treatments were grouped by:

- Number of anticancer drugs in the regimen. It was anticipated that the higher the number of drugs used, the higher the likelihood of toxicity, as the side effect profiles of the drugs would be additive.
- Commissioning status of the regimen. This was either baseline commissioned treatment or cancer drugs fund commissioned. It was felt that any differences in tolerance to treatments by commissioning status would be an interesting finding for clinical practice.
- Emetogenicity of the regimen in accordance with international guidelines (Hesketh *et al.,* 2017a). This was anticipated to reveal differences in nausea and vomiting, but admission rates were of particular interest with respect to emetogenicity and also the effect of emetogenicity on toxicities other than nausea and vomiting.

- Cytotoxic status of agents. Treatments were grouped as cytotoxic, non-cytotoxic or mixed. This was expected to highlight any differences between the traditional cytotoxic chemotherapy and the targeted therapies.
- BNF class of drug (Baxter, 2018). It was anticipated that the class of drug would have an impact on toxicity, as class effects could exist.

The first part of the analysis was to consider the overall incidence of toxicity across all treatments and all disease states.

The following primary outcome measures were investigated:

- Toxicity as a binary measure (experienced or not experienced). It was necessary to create a new variable in SPSS® of toxicity, which included all of the toxicities reported and enabled the number of patients reporting a toxicity of any grade to be collated.
- Grade of toxicity. This also necessitated the creation of a new variable in SPSS®, that grouped together all toxicities of the same grade.
- Hospital admission within 30 days of chemotherapy as a binary measure (admitted or not).
- Length of stay for those patients admitted

The following sub-group analyses were explored:

- The three diseases for which chemotherapy was given most commonly. These were explored as sub-populations for breast, colorectal and lung cancer, looking at the outcomes as in the whole population.
- Individual toxicities as a sub-analysis of the three most commonly reported toxicities. Nausea, vomiting and fatigue were investigated with the factors contributing to them being explored.

Analysis of the factors affecting toxicity was undertaken. The literature highlighted various factors that were thought to influence toxicity. These were

considered as potential predictors of toxicity along with others. The following independent variables were considered for their effect on occurrence of toxicity, grade of toxicity experienced and hospitalisation within 30 days of chemotherapy:

- Age, as a continuous variable and as a categorical variable
- ECOG performance status (Oken *et al*., 1982)
- Treatment used (drug regimen), grouped according to
    - BNF class
    - Emetogenicity
    - Cytotoxicity
    - Number of drugs
    - Commissioning status
- Disease being treated, according to disease group
- Intent of treatment (adjuvant, neoadjuvant or palliative)

Descriptive statistics were used to elucidate any initial relationship or correlations, with Pearson's X^2 test being used for the binary outcome measures (toxicity and admission) and Kruskall-Wallis test being used in the ordinal datasets (grade of toxicity). Length of stay was continuous data and so Kruskall-Wallis was used to test the significance of any variance. Where possible the correlation coefficient was calculated.

Regression analysis was undertaken. Multivariable logistic regression was used to explore the relationships between the predictors and toxicity and between the predictors and hospital admission. Ordinal logistic regression analysis was used to explore the relationships between the predictors and grade of toxicity. Regression analysis was not used to explore length of stay as it was felt to be too complex. Only descriptive statistics were used in this situation. Multivariable regression was undertaken following individual regression analysis and descriptive statistics, which were used to establish any possible relationships between predictors and outcomes. Only those variables that the individual analyses showed to have an effect on the outcome, were

included in the multivariable regression. It was also necessary to exclude some of the fields for certain predictors that had very small numbers of patients.

ECOG performance status was treated as ordinal data and explored accordingly. Intent of treatment was nominal data.

The probable sample size for the database was well over the anticipated size of 1000 patients. The anticipated four larger tumour groups, breast, lung, colorectal and urology, provided the most data and as such allowed for more in depth analysis. Regression analysis was used to explore in depth for breast, lung and colorectal diagnoses but urology was not included due to low rates of toxicity reporting and low patient numbers.

Hospital admission was of particular interest. Hospital admission figures were obtained from the trust patient administration system by a data analyst. Reason for admission was reported on the system as well as length of stay, and the data was linked to Chemocare®4 information regarding chemotherapy and a spread sheet produced of those patients admitted within 30 days of the first cycle of chemotherapy. The data was then reviewed manually and any admissions for reasons other than chemotherapy toxicity excluded. This data was then transferred to the main database for input into SPSS®. It was beyond the reaches of this research to calculate the exact cost of an admission, however it was anticipated that it may have be possible to look at local and national tariffs to perform a top down costing.

Length of stay was assessed and admissions analysed to identify any common contributing factors in a similar way to the occurrence of toxicity. The cut off of 30 days was used, as it mirrored one of the measures investigated in the national NCEPOD report (Mort *et al.* 2008). Care was taken to ascertain the reason for admission as it was recognised that patients may be admitted for various reasons in the prescribed period and indeed reasons for admission can

be multi-factorial. Only admissions due to symptoms of chemotherapy toxicity were explored. In every case, it was not clear if admission was due to toxicity or other causes of those symptoms. Length of stay was explored using descriptive statistics to identify any differences between the groups of patients when considering the different predictors.

Sub-group analyses were also undertaken. The three largest disease groups were explored as sub-populations and compared to each other and the population as a whole. The effect of the predictors on the outcomes used when looking at the whole population were used to look at the sub-populations and the same regression analysis was applied where appropriate. The three most commonly reported toxicities were also explored as individual secondary outcomes. It was necessary to create new variables for each toxicity, in order to investigate them as binary variables, as occurred and did not occur. The grades of the toxicities were also explored and regression analysis was applied where appropriate, in the same way as was done for the primary outcome measures. Admission rates and length of stay was also explored within each toxicity.

The structure of the analysis strategy is summarised in **table 7**.

Table 7. Analysis Strategy

	Outcome			
	Toxicity	**Severity**	**Admission**	**Length of stay**
Predictor				
Age Categorical				
Descriptive				
Univariable				
Multivariable				
Age Continuous				
Descriptive				
Univariable				
Multivariable				
PS				
Descriptive				
Univariable				
Multivariable				
Disease				
Descriptive				
Univariable				
Multivariable				
Intent				
Descriptive				
Univariable				
Multivariable				
Treatment - Cytotoxicity				
Descriptive				
Univariable				
Multivariable				
Treatment - Number of Drugs				
Descriptive				
Univariable				
Multivariable				
Treatment - Commissioning				
Descriptive				
Univariable				
Multivariable				
Treatment - Emetogenicity				
Descriptive				
Univariable				
Multivariable				

3.3 Exclusions

Due to the nature of the service implemented by the CATT team there were various exclusions. Patients who received their first cycle of chemotherapy as an inpatient did not receive a phone call, as most would still be an inpatient the day following chemotherapy. The consequence of this was that most patients with certain diagnoses were not included in the data as most of the chemotherapy given was given as an inpatient. This included germ cell tumours and sarcoma. It was anticipated that small numbers of patients with these diagnoses would be included in the data. Renal cell and melanoma patients have a dedicated clinical nurse specialist at NUH and as such receive their first cycle phone call from the clinical nurse specialist, who did not record the toxicity assessment in the CATT team's database. As such very few of these patients were included in the analysis.

As the study only collected data on toxicity within 24 hours of chemotherapy, only acute toxicity was assessed in the study. No long term, chronic or late effects are included in the data, as there was no mechanism in place to collect such data at NUH.

When completing toxicity assessments, the CATT team found that some patients were unreachable by telephone. The number of these patients was not recorded, but speaking to the CATT team, the nurses stated that this number is minimal.

Oral chemotherapy included in the data raised an interesting question. With parenteral regimens, the entire dose had been administered by the time of the telephone call. With oral chemotherapy, often only one or two doses may have been taken, out of a 21 or 28-day cycle. It is likely that few toxicities would have occurred at the time of the telephone call, as drug exposure would have been minimal and steady state serum concentrations not reached.

Gender was not recorded in the database when nurses completed the telephone call. As such, it was not possible to include gender in the analysis to investigate its effects on the outcome measures. To enter gender would have meant reviewing each record individually, which was felt to be too time consuming for this study.

The CATT team is an oncology service and is not currently extended to haematology patients at NUH, so no patients receiving chemotherapy for a haematological malignancy were included in the data.

Paediatric chemotherapy is delivered at Queen's Medical Centre, the other campus of NUH. It is delivered by a dedicated specialist team. As such, paediatric chemotherapy was not included in the data.

Incomplete entries in the database were excluded from analysis.

Some patients may have been admitted to hospital within 30 days of chemotherapy, but to a different hospital trust other than NUH. NUH is a regional centre and as such covers a large population of 3.5 million people for provision of specialist services (Nottingham University Hospitals, 2014). This means that geographically, it may result in hospital admissions to other trusts. This admission data is not readily available, hence only admissions to NUH were included in the data.

Fever and extravasation were reported as yes or no. As they were not graded as other toxicities were, they were not included in analysis.

Only toxicities in the UKONS 24 hour triage tool were included in the assessment. A free text box was available for nurses to add in any other toxicity not covered, however this was not included in the analysis.

Some sub-groups of the population had very small numbers of patients and as such it is not possible to draw robust conclusions about these groups.

3.4 Ethics

Data pertaining to patients was being used in this research and so it was essential to ensure that the appropriate ethical approval had been sought and granted. Ethics approval was sought from the University of Bradford and also from Nottingham University Hospitals NHS trust. Both ethics committees required the approval of the other in order to grant approval to the research. Data was collected as part of an NHS service in order to assess that service. Data was not being collected solely for the purpose of research. For the purposes of research, data was anonymised and patients were not identifiable. Data stored on a personal computer did not contain any patient identifiers, and was held on a password protected device, with a password protected document. As such, consent was not sought from patients. In no way did the research have any effect on the patients whose data was used. The research had the potential to make recommendations to practice and as such may have eventually had an effect on patient treatment decisions. Any recommendations made would be thoroughly evidence based.

A University of Bradford Ethics Checklist was completed and is attached in appendix 3. This confirms that full ethical approval from the University ethics committee was not required as the data was being collected as part of a service and was anonymised for the purposes of research.

A new approval process for NHS research was being rolled out by the Health Research Authority (HRA) (Health Research Authority, 2015) at the time of submitting the research proposal. However at the time of writing, this research fell into a category which could not yet be approved by the HRA so the traditional channels of approval were followed. In order to ascertain what ethical approval was required from the NHS an IRAS checklist was completed on the Health Research authority website (Health Research Authority and Medical Research Council, 2015b.). The checklist confirmed that this study would be considered research and so the next step was to decide if NHS research ethics committee (REC) approval was required. In order to do this,

another decision tool was used. Completion of the NRES tool (Health Research Authority and Medical Research Council, 2015b) indicated that REC approval was not required. However, as the study was being conducted at Nottingham University Hospitals, approval from the research and development department was required, so a copy of the proposal was submitted and no research undertaken until confirmation from research and development of approval. NUH required that an IRAS form be submitted, so this was completed and can be found in appendix 4. The dataset was already in existence by this time, but it was maintained on NUH trust computers and not removed from the hospital site, as data was collected by the CATT nurses, as part of a service. Once ethical approval was granted, data was anonymised on trust IT infrastructure, it was then transferred to a personal computer for analysis in a password protected document on a password protected device. At no point could any patient be identified from the data once this had happened. This was in accordance with NUH information governance regulations.

The IRAS identification number for this study was 179907.

4.0 Results

4.1 Population and Descriptive Statistics

A total of 1577 patients had data recorded from the call back service from January to December 2015. Some patients did not have complete entries in the database so these were excluded from analysis. This gave a population of 1539 (97.6%) for analysis. The mean age of the population was 63.2 years (SD = 11.4) and median age of the population was 65 years old (range 24 to 90). The distribution of the age of the population had a minimum value of 24 years, first quartile 56, median 65, third quartile 71.25 and a maximum of 90.

A histogram (**figure 2**) demonstrated the distribution of age, which was slightly negatively skewed, however age would not be expected to be normally distributed.

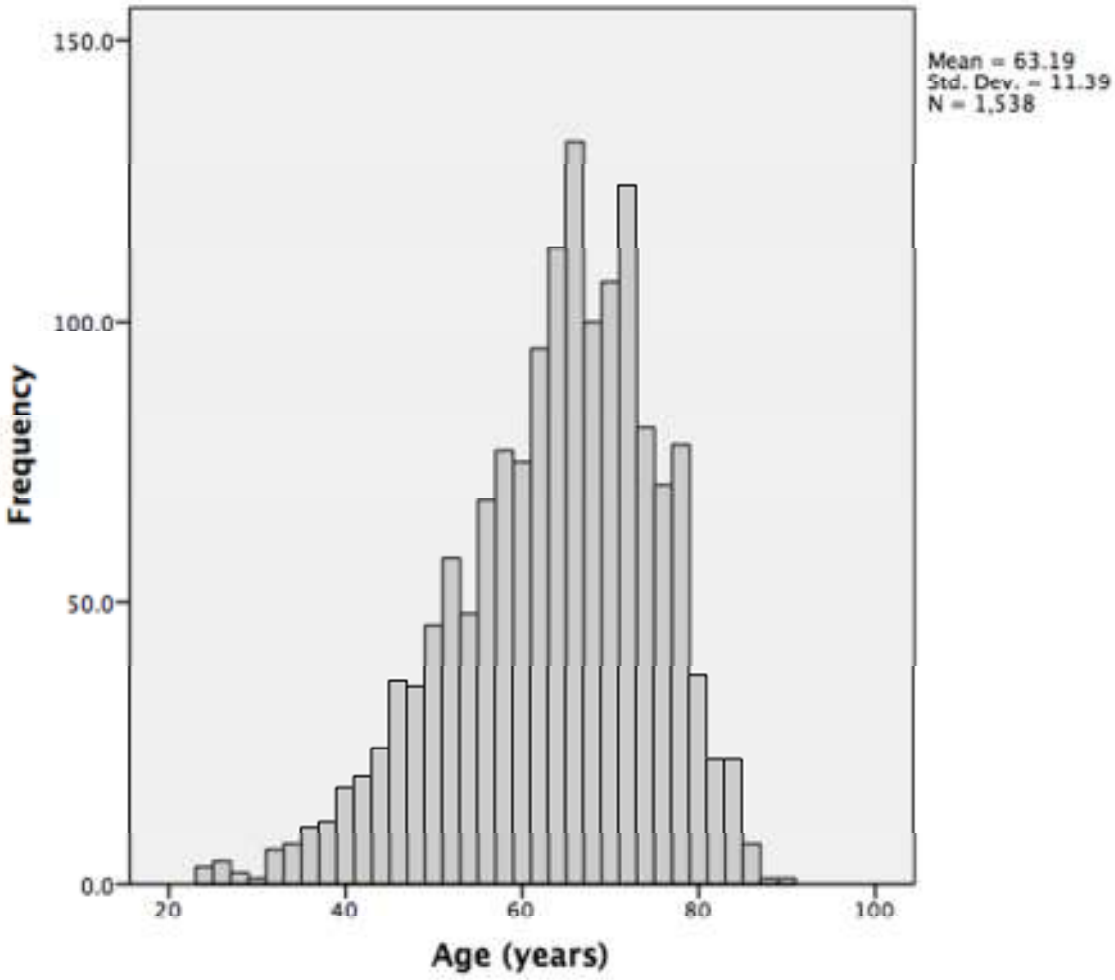


Figure 2. Age of Study Population

As seen in **Figure 2**, there was a wide variance in the age of patients treated.

Table 8. Age and Performance Status

			Age Group (years)						Total
			21-40	41-50	51-60	61-70	71-80	>80	
Performance status	0	n	33	111	174	262	179	23	783
		%	54.1	69.4	53.5	48	46.3	43.4	51.1
	1	n	25	40	128	255	185	25	658
		%	41	25	39.4	46.7	47.8	47.2	42.9
	2	n	3	9	21	26	22	5	86
		%	4.9	5.6	6.5	4.8	5.7	9.4	5.6
	3	n	0	0	2	3	1	0	6
		%	0	0	0.6	0.5	0.3	0	0.4
Total			61	160	325	546	387	53	1533

Table 8 showed the relationship between age and performance status. A higher proportion of older patients had a higher performance status at the start of treatment than in younger patients. Conversely the youngest patient group had the highest proportion of PS 0 patients compared to other age groups. As age increased, so did performance status. Spearman's test gave a correlation coefficient of 0.09 (p=0.01), suggesting a slight positive correlation between age and performance status.

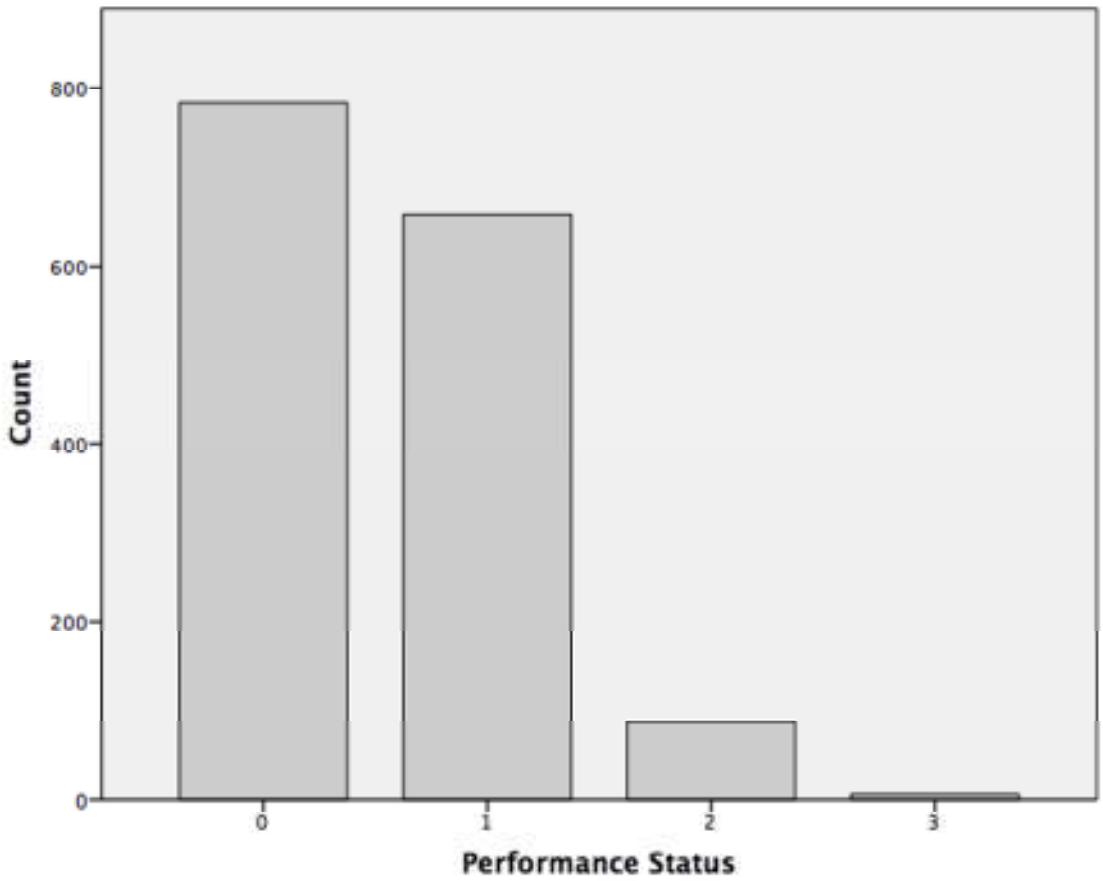


Figure 3. Performance Status of Study Population

Table 9. Performance Status of Study Population

		n	Valid %
Performance status	0	783	51.1
	1	658	42.9
	2	86	5.6
	3	6	0.4
Total		1533	100

The ECOG performance status at the time of administration was recorded and had the distribution as described in **Figure 3** and **Table 9**. The majority of patients were PS 0 or 1. There were very small numbers of patients with a performance status higher than 1 and no patients were performance status 4, making the size of the groups fairly uneven.

Chemotherapy was used to treat 38 different cancer diagnoses. As predicted, breast, colorectal and lung cancer were the most frequently treated tumour sites. For the purposes of data analysis, the diseases were grouped according to body system.

Table 10. Distribution of Patients in Disease Groups

		n	Valid %
Disease	Breast	438	28.5
	Colorectal	329	21.4
	Lung	242	15.7
	Upper GI	170	11.1
	Gynaecology	151	9.8
	Urology	107	7
	Head&Neck	47	3.1
	CNS	39	2.5
	Sarcoma	12	0.8
	CUP	1	0.1
	Skin	2	0.1
	Total	1538	100
	Missing	1	
Total		1539	

Table 11. Intent of Chemotherapy Given

		n	Valid %
Intent of Chemotherapy	Palliative	833	54.2
	Adjuvant	464	30.2
	Neoadjuvant	239	15.6
	Total	1536	100
	Missing	3	
Total		1539	

Just over half of treatments were palliative, meaning that the remaining treatments were of curative intent.

In the studied population, 118 different anticancer treatments were received, including multi-drug and single agent regimens. The most common regimen used was FEC75, which is used in breast cancer (East Midlands Cancer Alliance 2018). Treatments were grouped in various different ways for analysis and comparison.

The first method was to group into cytotoxic, non-cytotoxic and mixed chemotherapies. Cytotoxic treatment was given in 1422 (92.4%) of cases, non-cytotoxic accounted for 51 (3.3%) of treatments and 66 (4.3%) of treatments were a combination of cytotoxic and non-cytotoxic drugs.

The second way the treatments were grouped was by number of anticancer drugs contained within the regimen as shown in **Table 12**.

Table 12. Treatment Grouped by Number of Drugs

		n	Valid %
Number of Drugs	1	560	37
	2	533	35.2
	3	420	27.8
	Total	1513	100
	Missing	26	
Total		1539	

There was a fairly even distribution amongst the groups.

A third way of categorising the treatment used was to divide the them into those subject to baseline commissioning and those funded by the cancer drugs fund (CDF) as shown in **Table 13**.

Table 13. Commissioning Status of Treatment

		n	Valid %
Commissioning Status	Baseline	1432	93.1
	CDF	106	6.9
	Total	1538	100
	Missing	1	
Total		1539	

Only a small number of treatments were funded by the CDF, with the majority of treatments being baseline commissioned, which made the sizes of the groups extremely uneven.

The next way the treatments were grouped was by drug class, according to BNF classifications as shown in **Table 14** (Baxter, 2018).

Table 14. Treatment Grouped by Drug Class

		n	Valid %
Drug Class	Platinum	586	38.1
	Antimetabolites	527	34.3
	Taxane	133	8.6
	Topoisomerase I inhibitor	100	6.5
	Other	73	4.7
	Monoclonal Antibodies	45	2.9
	Alkylating Agent	30	2
	Anthracycline/Cytotoxic Antibiotic	23	1.5
	Vinca Alkaloid/Etoposide	19	1.2
	Immune therapy	2	0.1
	Total	1538	100
	Missing	1	
Total		1539	

The method of grouping in SPSS® was not reliable. Only one drug class was assigned to each patient, but many patients received more than one agent, so this could not be used to produce reliable data. It was therefore omitted from further analysis.

Drugs are frequently grouped in practice by emetogenic potential (Hesketh *et al.,* 2017a). There were a number of sources that provide classifications of drugs by emetogenicity. For the purposes of this research, the ASCO classification was used (Basch *et al.,* 2011).

Table 15. Treatment Grouped by Emetogenicity

		n	Valid %
Emetogenicity	Moderate	544	37.5
	High	464	32
	Low	409	28.2
	Minimal	33	2.3
	Total	1450	100
	Missing	89	
Total		1539	

There was a fairly even distribution of patients amongst the groups of treatments, with the exception of the minimal group, which only had a small number of patients.

Table 16. Grades of Toxicity Reported

		n	Valid %
Toxicity Grade	0	976	64.8
	1	434	28.8
	2	89	5.9
	3	6	0.4
	4	1	0.1
	Total	1506	100
	Missing	33	
Total		1539	

Table 16 showed the number of toxicities that were experienced and the percentage of patients reporting that grade of toxicity. The majority of patients did not report any toxicity (grade 0). Grade 1 toxicities were reported by 434 (28.8%) of patients and accounted for 81.9% of the total toxicities reported (i.e. grades 1-4), with 16.8% being grade 2, 1.1% being grade 3 and only 1 patient reporting a grade 4 toxicity (0.2%). This made the distribution between the groups fairly uneven. At least one any grade toxicity was reported by 35.6% of

patients.

Table 17. Percentage of Patients Reporting Each Grade of Toxicity

			Number Experiencing Grade of Toxicity (% of Total Patients Who Experienced Toxicity >grade 0)			
		Number of Patients Who Reported Any Grade (%)	1	2	3	4
Toxicity	Nausea	249 (15.9%)	214 (13.9%)	28 (1.8%)	3 (0.2%)	
	Fatigue	159 (10.%)	151 (9.8%)	8 (0.5%)		
	Vomiting	89 (5.8%)	52 (3.4%)	35 (2.3%)	2 (0.1%)	
	Constipation	60 (3.9%)	46 (3.0%)	14 (0.9%)		
	Arthralgia / Pain	49 (3.2%)	40 (2.6%)	9 (0.6%)		
	Sensory Neuropathy	55 (3.6%)	53 (3.4%)	2 (0.1%)		
	Diarrhoea	49 (3.2%)	43 (2.8%)	5 (0.3%)	1 (0.1%)	
	Anorexia	38 (2.5%)	25 (1.6%)	12 (0.8%)	1 (0.1%)	
	SOB	11 (0.7%)	8 (0.5%)	2 (0.1%)		1 (0.1%)
	Stomatitis	9 (0.6%)	8 (0.5%)	1 (0.1%)		
	Bleeding	2 (0.1%)	1 (0.1%)	1 (0.1%)		
	Motor Neuropathy	2 (0.1%)	2 (0.1%)			
	Bruising	0 (0%)				

Grade 1 toxicities were by far the most common of the toxicities reported, with

only a single grade 4 toxicity reported. Nausea, vomiting and fatigue were the most frequently reported toxicities Fever was reported by 1.9% of patients and extravasation by 3 patients (0.2%). These were not reported by grade so were not included in the analysis.

4.2 Primary Outcome Measures

The various factors that were thought to predict the outcomes of toxicity, grade of toxicity, admission and length of stay were explored.

4.2.1 Toxicity

Toxicity was explored as a binary variable; experienced or not and included any toxicity that was reported. The various predictors were investigated to ascertain their effect on the occurrence of toxicity.

4.2.1.1 Toxicity and Age

The relationship between age and the occurrence of any grade toxicity was explored. The age group reporting the most toxicities was the 51-60 year olds, who had a rate of 38.2% toxicity (123 patients). However, this rate did not differ greatly from other groups and a χ^2 test shows that there was no significant difference in the overall rate of toxicity reporting between age groups (χ^2=3.7 (p=0.599)).

The mean age of patients experiencing a toxicity of any grade was 62.8 years (SD=11.1) compared to 63.3 years (SD=11.6) for those experiencing no toxicity. There was little difference between these values.

4.2.1.2 Toxicity and Performance Status

Table 18. Toxicity Rate by Performance Status

		Number experiencing toxicity	% of Performance Status Group
Performance status	0	306	39.5%
	1	210	35.4%
	2	25	29.1%
	3	1	16.7%
Total		542	35.7%

Pearson's X^2=10.59 (p=0.01)

The number of patients experiencing a toxicity of any grade reduced as performance status increased. Spearman's correlation coefficient is –0.082 (p<0.01) suggesting a statistically significant negative correlation.

Table 19. Logistic Regression of Toxicity and Performance Status Controlled for Age

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Toxicity	Age (continuous)	-0.002	0.005	0.659	0.998	0.989	1.007
	Performance Status			0.019			
	1	-0.301	0.112	0.007	0.74	0.594	0.922
	2	-0.462	0.249	0.063	0.63	0.387	1.026
	3	-1.18	1.098	0.283	0.307	0.036	2.644
	Constant	-0.299	0.302	0.323	0.742		

Pseudo R^2<0.01

Table 19 used performance status 0 as the reference group and suggested that patients with performance status 1 were 26% less likely to experience a toxicity than those who were performance status 0. The effect for performance status 2 was of a similar magnitude but was of borderline statistical significance (p=0.06). The performance status 3 group was small, so not powered to establish a predictive relationship. Pseudo R^2, suggested a minimal effect

4.2.1.3 Toxicity and Disease

Table 20. Toxicity Rates and Disease

		Number experiencing toxicity	% of Disease Group
Disease	CNS	13	33%
	Skin	1	50%
	Upper GI	74	44.3%
	Breast	186	42.9%
	Colorectal	116	36.4%
	Head&Neck	16	34%
	Gynaecology	49	32.5%
	Urology	25	26.6%
	Lung	61	25.4%
	Sarcoma	1	8.3%
	CUP	0	0%
Total		542	35.7%

Pearson's X^2=38.47 (p<0.01)

Toxicity appeared highest in the breast, upper GI and colorectal groups and a Pearson's χ^2 test suggested that the differences between these groups was significant (p<0.01).

As CUP, Skin and Sarcoma groups had small numbers of patients, these were excluded from any regression analysis, as it would not be possible to draw any conclusions from such small numbers.

Table 21. Logistic Regression Analysis for Toxicity and Disease Controlled for Age

						95% C.I.for EXP(B)	
		B	S.E.	Sig.	Exp(B)	Lower	Upper
Toxicity	Age (continuous)	0.001	0.005	0.81	1.001	0.991	1.011
	Disease			0			
	CNS	0.501	0.417	0.229	1.651	0.729	3.737
	Breast	0.895	0.254	0	2.447	1.488	4.026
	Colorectal	0.622	0.258	0.016	1.862	1.123	3.087
	Gynaecology	0.449	0.289	0.12	1.567	0.89	2.759
	Head and Neck	0.526	0.387	0.174	1.692	0.793	3.609
	Upper GI	0.952	0.277	0.001	2.59	1.504	4.462
	Lung	0.102	0.273	0.709	1.107	0.649	1.89
	Constant	-1.26	0.421	0.003	0.284		

Pseudo R^2 =0.02

The regression analysis in **Table 21** used urology as the reference group. Breast cancer patients appeared 145% more likely to experience a toxicity than urology cancer patients ($p<0.01$) and upper GI cancer patients 159% more likely ($p<0.01$). Pseudo R^2 suggested that the analysis explained some of the variance in toxicity, but there was still a great deal unexplained, which could mean that other variables played a role in explaining that variance and thus had an effect on toxicity.

4.2.1.4 Toxicity and Treatment Intent

There was little difference in the percentage of patients experiencing a toxicity between the different treatment intents, although neoadjuvant patients had a higher rate of toxicity reporting than palliative and adjuvant patients. However the differences between the groups was not statistically significant according to Pearson's χ^2 ($p>0.1$).

4.2.1.5 Toxicity and Treatment

As described above, treatments were grouped by different methods for the purposes of analysis.

When grouped according to cytotoxicity, the group who received a combination of drugs reported the highest rate of toxicity and the lowest rate of any grade toxicity was in the non-cytotoxic group, but the differences were not statistically significant ($p>0.1$). The groups were not evenly distributed and as such any comparison would be difficult.

Table 22. Toxicity Rates by Treatment Grouped According to the Number of Drugs

		Number experiencing toxicity	% of Treatment Group
Number of Drugs	3	203	49.0%
	2	173	35.7%
	1	157	28.5%
	Missing	9	
Total		542	35.7%

Pearson's $\chi^2=46.4$ ($p<0.01$)

Table 22 showed the rate of toxicity by the number of drugs contained in the regimen. The highest reporters of toxicity were those patients who received a combination containing 3 drugs. It appeared that as the number of treatments increased, so did the number of toxicities. A Spearman's correlation coefficient was calculated as 0.163 ($p<0.01$) suggesting a positive correlation that is statistically significant.

Table 23. Logistic Regression Analysis of Toxicity and Treatment Grouped by the Number of Drugs

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Toxicity	Age (continuous)	0.004	0.005	0.432	1.004	0.994	1.014
	Number of drugs			0			
	1	-0.896	0.139	0	0.408	0.311	0.536
	2	-0.701	0.138	0	0.496	0.378	0.651
	Constant	-0.273	0.308	0.376	0.761		

Pseudo R^2 = 0.03

Pseudo R^2 in **table 23** suggested that the data explained a small amount of the variance in toxicity. The 3-drug group was used as the reference as it was the largest group. The analysis suggested that patients on two drugs were 50% ($p<0.01$) less likely to experience a toxicity, compared to those receiving three drugs and those on one drug were 59% ($p<0.01$) less likely to experience a toxicity than those on a single agent. The data would suggest that the more drugs used, the more likely a toxicity is to occur.

When grouped according to commissioning status, there appeared to be no statistically significant difference in the percentage of patients reporting a toxicity between the groups ($p>0.1$).

Table 24. Toxicity Rate and Treatment Grouped by Emetogenicity

		Number experiencing toxicity	% of Treatment Group
Emetogenicity	High	197	42.9%
	Moderate	188	34.9%
	Low	122	30.6%
	Minimal	7	21.2%
	Missing	28	
Total		542	35.70%

Pearson's χ^2 = 18.07 (p<0.01)

It should be noted that in **table 24** this was any toxicity of any grade and not just limited to nausea and vomiting. Toxicity was clearly reported more frequently by those patients receiving highly emetogenic chemotherapy.

Table 25. Logistic Regression Analysis of Toxicity and Treatment Grouped by Emetogenicity

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Toxicity	Age (continuous)	0.001	0.005	0.81	1.001	0.992	1.011
	Emetogenicity			0.001			
	Moderate	-0.337	0.131	0.01	0.714	0.552	0.923
	Low	-0.535	0.146	0	0.585	0.44	0.779
	Minimal	-1.029	0.437	0.019	0.357	0.152	0.842
	Constant	-0.361	0.31	0.244	0.697		

Pseudo R^2=0.012

Regression analysis used highly emetogenic treatments as the reference group, as it had a large number of patients and was clinically significant

($p<0.01$). All of the steps in the analysis were statistically significant ($p<0.01$). The analysis suggested that patients on moderately emetogenic chemotherapy were 29% less likely to experience a toxicity than those on highly emetogenic chemotherapy ($p=0.01$). Those on low emetogenic chemotherapy were 41% less likely to experience a toxicity ($p<0.01$) and those on minimally emetogenic chemotherapy, 64% less likely ($p=0.02$). The analysis only had a small effect on explaining the variance of toxicity.

4.2.1.6 Multivariable Logistic Regression of Toxicity

Multivariable logistic regression was undertaken of the above predictors, using only those predictors shown to have an effect on toxicity. These were performance status, diagnosis, treatment by drug class, treatment by emetogenicity and the number of drugs received. Age was controlled for.

Table 26. Multivariable Logistic Regression Analysis for Toxicity

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Age (continuous)		0.008	0.005	0.142	1.008	0.997	1.019
Performance Status				0.7			
	1	0.517	1.136	0.649	1.678	0.181	15.538
	2	0.379	1.134	0.738	1.461	0.158	13.494
	3	0.347	1.157	0.764	1.415	0.147	13.653
Disease				0.012			
	CNS	0.526	0.463	0.257	1.691	0.682	4.195
	Breast	0.597	0.312	0.055	1.817	0.987	3.347
	Colorectal	0.546	0.307	0.076	1.726	0.945	3.151
	Gynaecology	0.432	0.336	0.198	1.54	0.798	2.972
	Head & Neck	0.677	0.459	0.14	1.968	0.801	4.835
	Upper GI	0.781	0.33	0.018	2.183	1.143	4.168
	Lung	-0.066	0.331	0.842	0.936	0.489	1.791
Emetogenicity				0.942			
	High	0.238	0.531	0.654	1.269	0.448	3.592
	Moderate	0.258	0.503	0.608	1.295	0.483	3.472
	Low	0.171	0.494	0.729	1.187	0.451	3.124
Number of drugs		0.352	0.119	0.003	1.422	1.127	1.794
	1	-0.704	0.237	0.003	0.495	0.311	0.787
	2	0.374	0.209	0.073	0.688	0.457	1.036
Constant		-2.889	1.291	0.025	0.056		

Pseudo R^2 = 0.04

The multivariable logistic regression for toxicity controlled for age had pseudo R^2 =0.04 which was slightly larger than any of the values seen in the individual regression analyses. This value was still pretty small, but suggested that the analysis went some way to explaining the variance in toxicity. When all other variables were taken into account, age still had no statistically significant effect on toxicity (p>0.1). The analysis suggested the following:

- Breast cancer patients were 82% more likely to report a toxicity than urology cancer patients , this was of borderline statistical significance (p=0.06)

- Upper GI cancer patients were 118% more likely to see a toxicity than urology cancer patients (p=0.02)
- Patients who received 2 drugs were 31% less likely to experience a toxicity than those who received 3 drugs (p=0.07). This was of borderline significance.
- Patients who received 1 drug were 50% less likely to experience a toxicity than those who received 3 drugs (p<0.01).

The emetogenicity of a drug, did not yield any statistically significant relationships in the multivariable analysis, which might suggest an interaction of this variable with others (p>0.1).

4.2.2 Grade of toxicity

The grade of toxicity was explored in order to assess the severity of toxicities being reported. **Table 16** showed the frequencies of each grade of toxicity, with the majority of the population not reporting any toxicity (grade 0). These patients were still included in the analyses of toxicity severity, in order to maintain the statistical power of the data. The same predictors were investigated for severity of toxicity as were used to assess occurrence of toxicity. As there were only small numbers of grade 3 and 4 toxicities, these were too low to draw any conclusions from.

4.2.2.1 Age and Grade of Toxicity

Age was explored as a continuous and categorical variable.

Table 27. Mean Age of Patients Reporting Each Grade of Toxicity

		Mean age	N	Std. Deviation
Grade of toxicity	0	63.3	976	11.6
	1	63.2	433	10.8
	2	59.9	89	12.0
	3	68.3	6	3.4
	4	72.0	1	.
Total		63.1	1505	11.4

Kruskall-Wallis p=0.03

The age of patients experiencing a grade 2 toxicity was slightly lower than that of patients reporting a grade 1 toxicity. The grade 3 and 4 groups were too small to draw conclusions from. Kruskall-Wallis would suggest that these differences were statistically significant and that there was an effect on grade of toxicity from age (p=0.03).

There was no statistically significant correlation of age and grade of toxicity when using Spearman's correlation coefficient (p>0.1).

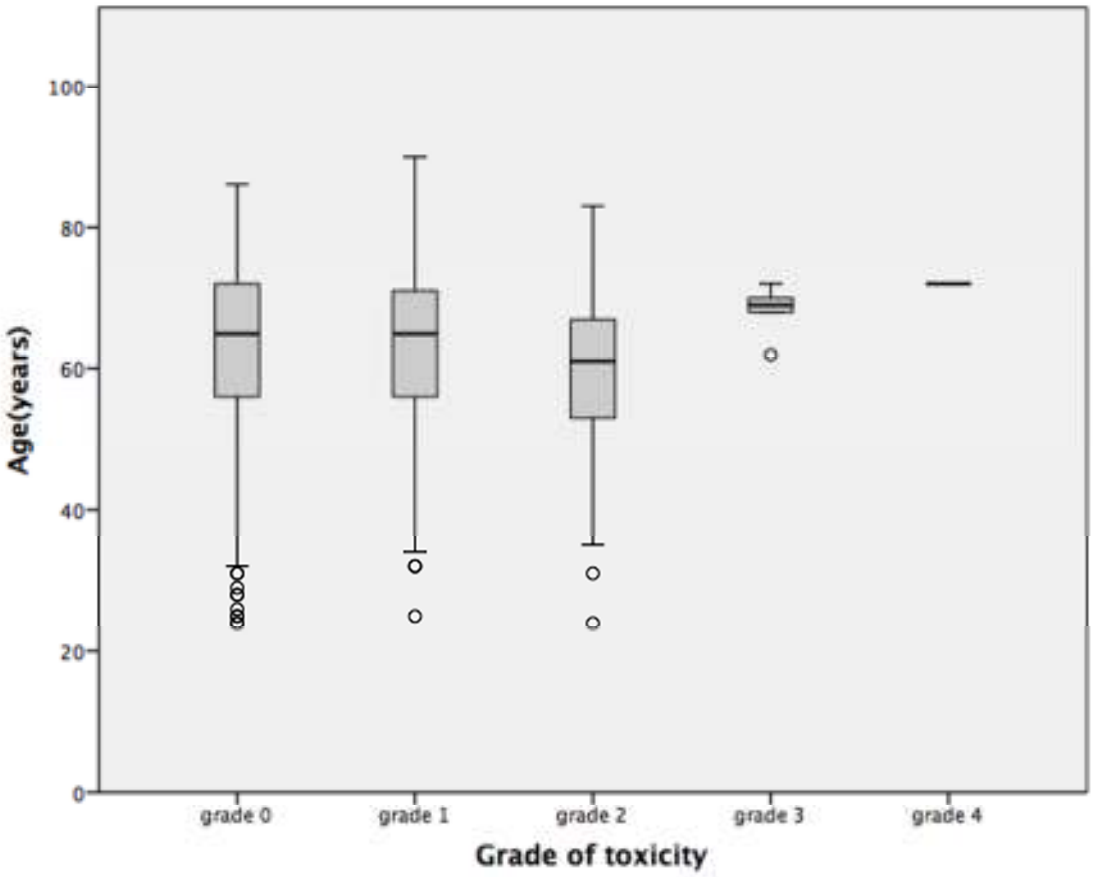


Figure 4. The Distribution of Age in Patients Reporting Each Grade of Toxicity

Figure 4 illustrated the similar means and standard deviations of age in each group of toxicity, suggesting that there was no large difference between the groups.

When age was grouped, the differences between the groups were not statistically significant ($p>0.1$). There appeared to be no pattern or a relationship between age as a continuous variable and grade of toxicity.

Table 28. Ordinal Logistic Regression Analysis of Grade of Toxicity and Age

	Grade of toxicity	B	Std. Error	Sig.	Exp(B)	95% Profile Likelihood Confidence Interval for Exp(B)	
						Lower Upper	Upper
Threshold	1	0.259	0.6177	0.674	1.296	0.392	4.445
	2	3.074	0.7116	0	21.637	5.563	91.436
	3	5.03	1.1681	0	152.96	21.61	3186.1
Age (continuous)		-0.02	0.0099	0.043	0.98	0.961	0.999

The analysis would suggest that as age increased, there was a slight decrease in the grade of toxicity experienced. An ordinal regression analysis for grade of toxicity and age, when grouped as a categorical variable showed no significant relationship ($p>0.1$).

4.2.2.2 Toxicity by Grade and Performance Status

As there were small numbers of patients in the performance status 3 and 4 groups, they were not included in the analysis.

Table 29. Grade of Toxicity and Performance Status

		Grade of Toxicity		
		0	1	2
Performance status	0	468 61.1%	254 33.2%	43 5.6%
	1	438 68.1%	159 24.7%	42 6.5%
	2	61 70.9%	19 22.1%	4 4.7%
Total		972	433	89

Pearson $\chi^2 = 34.95$ ($p<0.01$)

The rate of grade 1 toxicity seemed to decrease with performance status. There did not appear to be a pattern with grade 2 although, the rate of patients not experiencing toxicity increased with performance status. These differences did appear to be statistically significant ($p<0.01$). Univariable regression analysis did not yield any statistically significant data ($p>0.1$).

4.2.2.3 Grade of Toxicity and Disease

As with toxicity, skin, CUP and sarcoma were omitted for analysis, due to small numbers of patients. Grade 3 and 4 toxicities were also excluded due low numbers.

Table 30. Grade of Toxicity and Disease

		Grade of Toxicity		
		0	1	2
Disease	CNS	26 66.7%	8 20.5%	3 7.7%
	Breast	248 57.9%	149 34.8%	31 7.2%
	Colorectal	203 63.8%	98 30.8%	16 5%
	Gynaecology	102 68%	41 27.3%	7 4.7%
	Head&Neck	31 67.4%	13 28.3%	2 4.3%
	Upper GI	93 56.4%	56 33.9%	13 7.9%
	Lung	179 74.9%	49 20.5%	10 4.2%
	Urology	81 77.1%	19 18.1%	5 4.8%
Total		963 64.6%	433 29.1%	87 5.8%

Pearson's $\chi^2=73.69$ ($p<0.01$)

The differences between the disease groups appeared statistically significant ($p<0.01$), but the relationship did not appear to be linear. An ordinal logistic

regression analysis of grade of toxicity with disease controlled for age, showed no statistically significant relationships ($p>0.1$).

4.2.2.4 Grade of Toxicity by Intent of Treatment

When considering the rates of each grade of toxicity by treatment intent, Pearson's χ^2 test suggested that the differences between the groups were not significant ($p>0.1$) and an ordinal regression analysis showed no significant predictions ($p>0.1$).

4.2.2.5 Grade of Toxicity and Treatment

The potential effect of treatment on the severity of toxicity was investigated, using the groupings as previously. None of the methods of grouping treatments revealed any statistically significant differences ($p>0.1$), apart from the number of drugs ($p=0.04$).

The rates of each grade of toxicity by treatment grouped according to the number of drugs in the regimen produced a Pearson's χ^2 test that revealed no statistically significant difference between the groups ($p>0.1$). However a Spearman's correlation coefficient was calculated as 0.168 ($p<0.01$), suggesting a positive correlation of number of drugs with grade of toxicity. An ordinal logistic regression analysis suggested no significant predictions ($p>0.1$).

Table 31. Multivariable Ordinal Logistic Regression of Grade of Toxicity

		B	Std. Error	Sig.	Exp(B)	95% Profile Likelihood Confidence Interval for Exp(B)	
						Lower	Upper
	Grade 4	-6.968	1.0466	0	0.001	5.14E-05	0.005
	Grade 3	-5.018	0.488	0	0.007	0.002	0.016
	Grade 2	-2.355	0.3262	0	0.095	0.05	0.179
	Grade 1	-0.236	0.3145	0.452	0.789	0.425	1.458
Age (continuous)		0.002	0.0051	0.73	1.002	0.992	1.012
Disease							
	Urology	0.843	0.2558	0.001	2.324	1.427	3.904
	CNS	0.24	0.3566	0.501	1.272	0.643	2.632
	Colorectal	0.235	0.1517	0.121	1.265	0.941	1.706
	Gynaecology	0.417	0.199	0.036	1.517	1.032	2.255
	Head & Neck	0.403	0.3248	0.215	1.496	0.806	2.903
	Upper GI	-0.118	0.1836	0.521	0.889	0.621	1.276
	Lung	0.73	0.181	0	2.075	1.462	2.974
	Breast	0a	.	.	1	.	.

The analysis in **Table 31** used grade 0 toxicity and breast cancer patients as a reference group. The analysis went some way to explain the variance in toxicity grade but still left a large amount of variance unaccounted for. No significant relationships between performance status and toxicity was identified in the analysis, which could suggest that there was a type I error when looking at the differences between performance status groups ($p>0.1$). It did, however, reveal some significant predictors of grade of toxicity. These were:

- Urology cancer patients reported on average an 84% higher grade of toxicity than breast cancer patients ($p<0.01$)
- Gynaecology cancer patients reported on average a 42% higher grade toxicity than breast cancer patients ($p=0.04$)
- Lung cancer patients reported on average a 73% higher grade toxicity than breast cancer patients ($p<0.01$)

Referring back to **Table 30** can help to further understand the regression analysis. The breast group was used as the reference group and had one of the lower percentages of grade 0 toxicities. Lung, gynaecology and urology cancer patients all had higher rates of grade 0 toxicity than breast. This was a complex analysis, but it suggested that disease had an effect on the severity of toxicity.

4.2.3 Hospital Admission

There were 203 admissions due to chemotherapy toxicity in the population studied. This translated as an admission rate of 13.1% across the entire population studied. The mean number of days after chemotherapy when patients were admitted was 8.2 (SD=5.4) and the mean length of stay was 4.4 days (SD= 4.4).

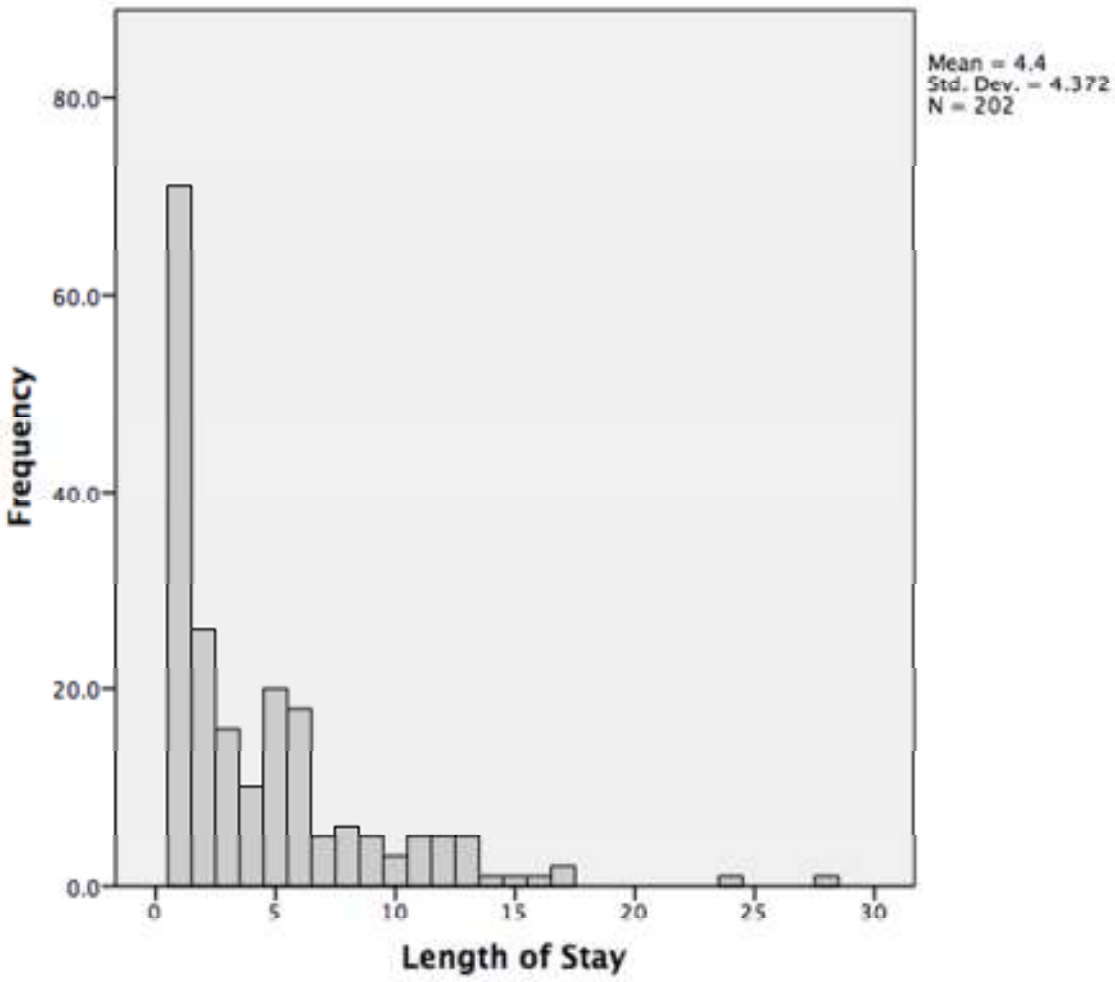


Figure 5. Length of Stay in Patients Admitted.

The histogram in **Figure 5** showed the distribution of length of stay, showing a positive skew. Median length of stay was 3 days with a range of 1 to 28 days.

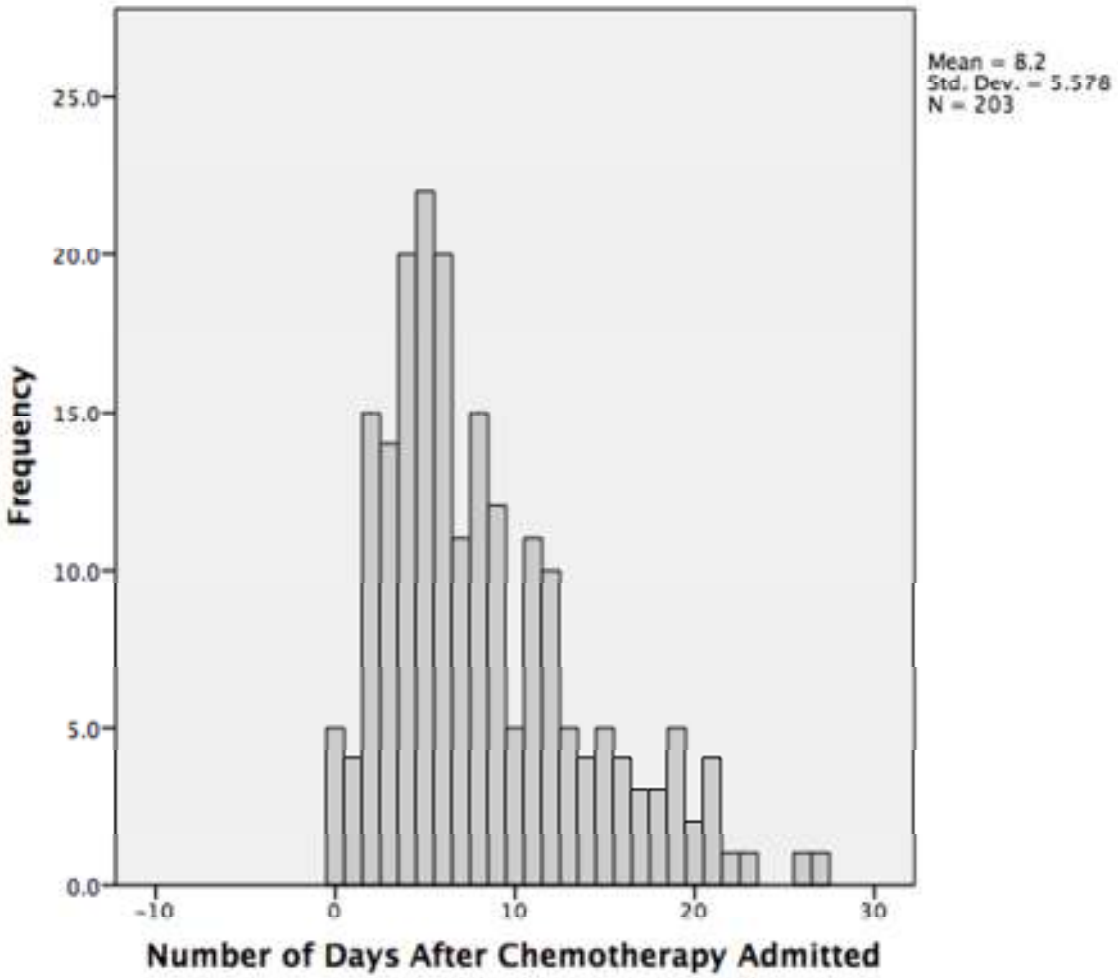


Figure 6. Number of Days After Chemotherapy Patients Were Admitted

The histogram in **figure 6** showed the distribution of the number of days after chemotherapy, patients were admitted. There was a peak at 5 days. The median number of days after chemotherapy patients were admitted was 7 with a range of 0 to 27.

Table 32. Reasons for Admission

Reason Admitted	n	Valid %
Pyrexia/?Neutropenic Sepsis	56	27.6
Multiple Reasons	25	12.3
Nausea and or Vomiting	20	9.9
Unknown	16	7.9
Abdominal Pain	11	5.4
Diarrhoea	10	4.9
SOB	8	3.9
Generally unwell	8	3.9
Diarrhoea and Vomiting	5	2.5
Collapse/Fall	4	2
Chest pain	4	2
Confusion	3	1.5
Urinary Symptoms	3	1.5
Pain	3	1.5
Bleeding	3	1.5
Acute Kidney Injury	3	1.5
Weakness/Lethargy	2	1
Leg Swelling	2	1
? Bowel Obstruction	2	1
Chest Infection	2	1
Cytopenia	2	1
Deranged LFTs	2	1
Dental	1	0.5
Mucositis	1	0.5
Pleural effusion	1	0.5
Neurological Symptoms	1	0.5
Dysphagia	1	0.5
Constipation	1	0.5
Skin problems	1	0.5
Dehydration	1	0.5
Reduced oral intake	1	0.5

Table 32 showed that there were 31 individual reasons for admission, showing a varied list of symptoms that could have been associated with disease or chemotherapy.

Hospital admission was treated as a binary variable with patients either being admitted or not admitted within 30 days of chemotherapy. The relationship

between the various predictors and hospital admission were studied.

4.2.3.1 Hospital Admission and Age

The mean age of patients admitted within 30 days of chemotherapy was 63 (SD= 10.9) years compared to a mean age of 63.2 years (SD= 11.5) for patients not admitted. Clearly there was no difference in mean age between the two groups.

When age was treated as a categorical variable, the rate of admission was lowest in the 41-50 age group and highest in the 51-60 age group. A χ^2 test showed that the differences between the age groups was not statistically significant ($p>0.1$).

4.2.3.2 Hospital Admission and Performance Status

The relationship between hospital admission and performance status was explored.

Table 33. Hospital Admission Rates and Performance Status

		Number admitted	% of Performance Status Group
Performance status	2	17	19.8%
	3	1	16.7%
	1	102	15.5%
	0	81	10.3%
	Missing	2	
Total		201	13.10%

Pearson's χ^2 = 11.97 (P<0.01)

The highest admission rate was in patients who were performance status 2 and

the lowest in patients who were performance status 0. Although these differences were statistically significant ($p<0.01$), a logistic regression analysis failed to identify any statistically significant predictions, suggesting that performance status as a whole was not a significant predictor of hospital admission ($p>0.1$). It is possible that this highlighted a type 1 error issue with the χ^2 test, which could falsely suggest that there were significant differences between the groups.

4.2.3.3 Hospital Admission and Disease

Table 34. Hospital Admission Rates and Disease

		Number Admitted	% of Disease Group
Disease	Head&Neck	10	21.3%
	Upper GI	31	18.2%
	Lung	44	18.2%
	Gynaecology	24	15.9%
	CNS	5	12.8%
	Colorectal	37	11.2%
	Breast	45	10.3%
	Urology	6	5.6%
	Missing	1	
Total		202	13.3%

Pearson's $\chi^2 = 22.3$ ($p<0.01$)

The highest rate of admission was seen in the head and neck cancer patients and skin, sarcoma and CUP had no admissions, although these groups all had small numbers of patients, so the sample may not have been representative of these populations. As such, skin, sarcoma and CUP were omitted from further analysis.

Table 35. Logistic Regression Analysis of Admission and Disease Controlled for Age

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Age (continuous)		-0.006	0.007	0.403	0.994	0.98	1.008
Disease				0.003			
	CNS	0.814	0.647	0.208	2.258	0.635	8.023
	Breast	0.598	0.455	0.189	1.818	0.746	4.433
	Colorectal	0.729	0.456	0.11	2.074	0.848	5.072
	Gynaecology	1.125	0.477	0.018	3.081	1.21	7.849
	Head&Neck	1.46	0.555	0.008	4.306	1.452	12.775
	Upper GI	1.301	0.466	0.005	3.673	1.475	9.147
	Lung	1.306	0.452	0.004	3.693	1.522	8.962
Constant		-2.411	0.647	0	0.09		

Pseudo R^2=0.015

The regression analysis in **Table 35** used urology as the reference group. The analysis suggested that gynaecology cancer patients had 208% increased chance of being admitted compared to urology cancer patients (p=0.02). Head and neck cancer patients appeared to have a 330% higher chance of admission compared to urology cancer patients (p<0.01). Upper GI cancer patients were 267% more likely to be admitted than urology cancer patients (p<0.01), and lung cancer patients 269% more likely to be admitted than urology cancer patients (p<0.01).

4.2.3.4 Hospital Admission and Intent of Treatment

There appeared to be little difference in the percentage of patients admitted within 30 days of the first cycle of chemotherapy according to treatment intent (p>0.1).

4.2.3.5 Hospital Admission and Treatment

The potential effect of treatment on hospital admission rates was investigated using the methods of grouping toxicity as before.

Table 36. Hospital Admission and Treatment Grouped According to Cytotoxicity

		Number Admitted	% of Treatment Group
Cytotoxicity	Mixed	12	18.2%
	Cytotoxic	189	13.3%
	Non-cytotoxic	1	2.0%
	Missing	1	
Total		202	13.1%

Pearson's χ^2 = 7.09 (p=0.03)

There was a large variance in admission rates in the number of patients in each group making comparison difficult. A higher percentage of patients receiving the combination chemotherapy were admitted than those who received other treatment.

Table 37. Logistic Regression Analysis for Hospital Admission and Treatment by Cytotoxicity

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Age (continuous)		-0.001	0.007	0.911	0.999	0.986	1.012
Cytotoxicity	-			0.068			
	Cytotoxic	-0.369	0.329	0.262	0.691	0.363	1.317
	Non-cytotoxic	-2.405	1.06	0.023	0.09	0.011	0.721
Constant		-1.459	0.516	0.005	0.233		

Pseudo R^2=0.06

The analysis in **Table 37** used mixed as the reference group. The analysis suggested patients on non-cytotoxic chemotherapy were 91% less likely to experience a toxicity compared to those on a combination regimen (p=0.02). The pseudo-R^2 value suggested that the analysis explains a small amount of the variance.

Table 38. Hospital Admission Rates and Treatment Grouped by Number of Drugs

		Number Admitted	% of Treatment Group
Number of Drugs	2	93	17.4%
	3	49	11.7%
	1	57	10.2%
	Missing	4	
Total		199	13.20%

Pearson's χ^2=13.76 (p<0.01)

The rate of admission was highest in those patients receiving two drugs and lowest in those receiving a single agent. The pattern of the relationship did not

appear to be linear but the differences were statistically significant (p<0.01).

Table 39. Logistic Regression Analysis for Hospital Admission and Treatment Grouped by Number of Drugs

	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
					Lower	Upper
Age (continuous)	-0.004	0.007	0.591	0.996	0.983	1.01
Number of Drugs -			0.001			
1	-0.135	0.21	0.52	0.873	0.579	1.318
2	0.489	0.194	0.012	1.63	1.114	2.385
Constant	-1.805	0.431	0	0.165		

Pseudo R^2=0.02

The analysis in **Table 39** suggested that patients on 2 drugs were 63% more likely to be admitted than those on 3 drugs (p=0.01).

When grouped according to commissioning status**,** a higher percentage of patients were admitted within 30 days of chemotherapy in the baseline commissioned group but this was not statistically significant (p>0.1).

Table 40. Hospital Admission Rates and Treatment Grouped by Emetogenicity

		Number Admitted	% of Treatment Group
Emetogenicity	Moderate	85	15.6%
	High	62	13.4%
	Low	44	10.8%
	Minimal	1	3.0%
	Missing	11	
Total		192	13.2%

Pearson's χ^2=7.9 (p=0.05)

In **Table 40**, the group who received chemotherapy of moderate emetogenicity had the highest rates of admission, however a logistic regression analysis was not able to show any statistically significant prediction about admission (p>0.1). This could suggest a type 1 error with the Pearson's χ^2 test.

4.2.3.6 Multivariable Logistic Regression of Admission

Table 41. Multivariable Logistic Regression of Hospital Admission

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Age (continuous)		-0.005	0.007	0.52	0.995	0.981	1.01
Number of Drugs				0.008			
	1	-0.153	0.241	0.526	0.858	0.535	1.376
	2	0.5	0.248	0.044	1.649	1.013	2.683
Disease				0.009			
	CNS	1.074	0.657	0.102	2.928	0.808	10.609
	Breast	0.741	0.476	0.119	2.099	0.826	5.331
	Colorectal	0.664	0.462	0.151	1.942	0.785	4.801
	Gynaecology	1.117	0.479	0.02	3.055	1.195	7.814
	Head & Neck	1.758	0.567	0.002	5.8	1.907	17.638
	Upper GI	1.335	0.476	0.005	3.799	1.493	9.665
	Lung	1.018	0.461	0.027	2.766	1.12	6.833
Constant		-2.634	0.676	0	0.072		

Pseudo R^2 = 0.02

A multivariable logistic regression for admission, using the variables shown to have an effect on admission rates, with groups excluded as in previous regression analyses and controlled for age was performed. The analysis contributed to the explanation of the variance in admission rates only minimally. The analysis suggested several predictions of statistical significance:

- Patients who received treatment with 2 drugs were 65% more likely to be admitted than patients on 3 drugs (p=0.04)
- Patients with gynaecological cancer were 206% more likely to be admitted than those with urological cancer (p=0.02)
- Head and neck cancer patients were 408% more likely to be admitted than those with urological cancer (p<0.01)
- Patients with an upper GI cancer were 279% more likely to be admitted than those with urological cancer (p<0.01)
- Patients with lung cancer were 177% more likely to be admitted than those with urological cancer (p=0.03

4.2.3.7 Toxicity and Admission

All admissions included in the data were due to symptoms of toxicity, however it was explored if this was affected by the reporting of toxicity at the point of the call back.

Table 42. Toxicity and Admission

		Number admitted	% of Toxicity Group Admitted
Toxicity	Toxicity	125	12.80%
	No Toxicity	77	14.20%
	Missing	1	
Total		202	13.20%

Pearson's χ^2=0.571 (p=0.45)

Table 42 showed that there was a higher rate of admission in the experienced a toxicity group, however this could not be considered statistically significant (p=0.45).

Table 43. Admission Rates for Each Grade of Toxicity

		Number Admitted	% of Grade Group Admitted
Grade of Toxicity	3	2	33.30%
	2	21	23.60%
	0	125	12.80%
	1	52	12%
	4	0	0%
	Missing	3	
Total		200	13.20%

Pearson's χ^2= 11.3 (p=0.02)

The admission rate appeared to increase as the grade of toxicity increased and Pearson's χ^2 test suggested that this was statistically significant (p=0.02). Regression analysis did not show any statistically significant predictions (p>0.1). This could have been as a result of a type 1 error or due to the low numbers in some of the groups, for example in the grade 3 and 4 toxicity groups there were very small numbers of patients. A sample size large enough to allow for more patients in the grade 3 and 4 groups would be needed in order to elucidate this further.

4.2.4 Length of stay

The effects of the predictors on length of stay were analysed**.**

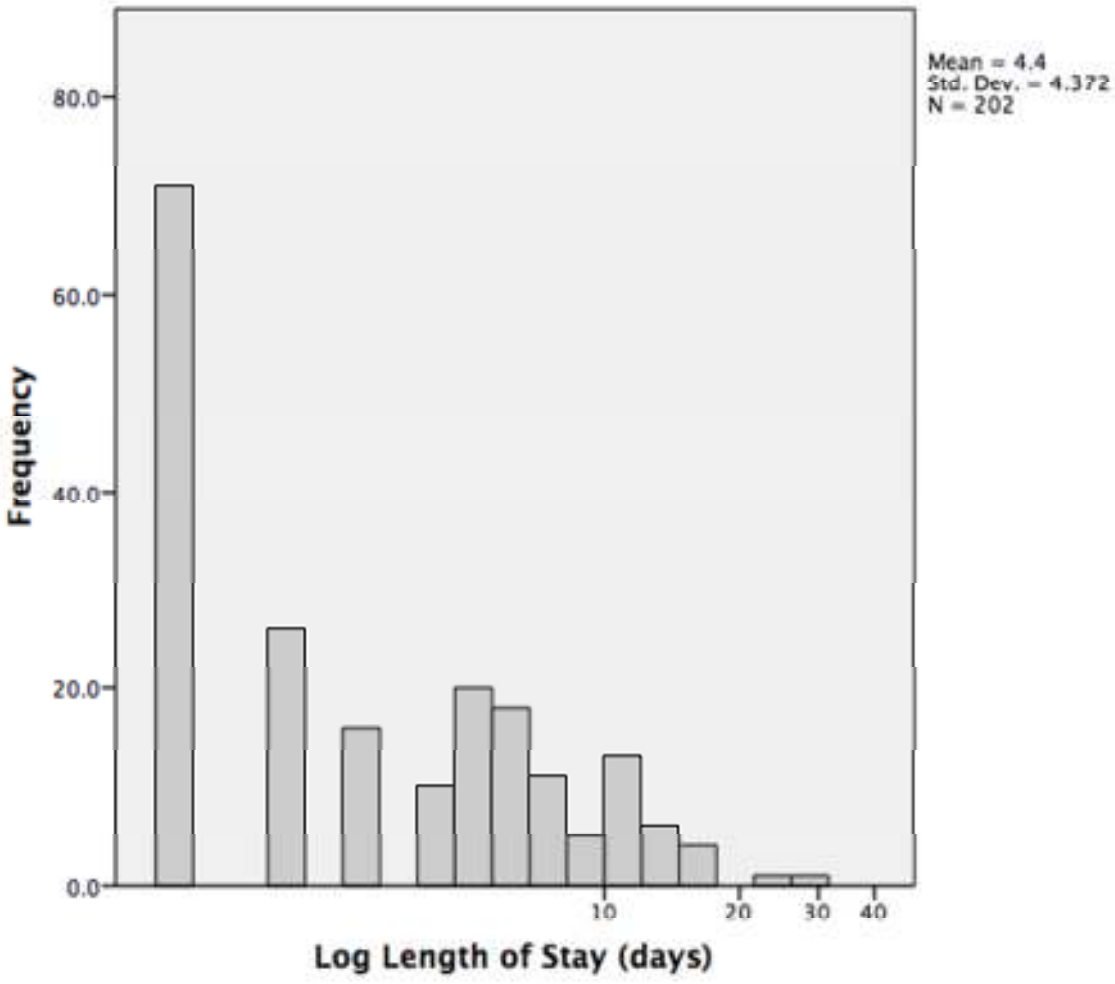


Figure 7. Distribution of Log Length of Stay

The histogram in **figure 7** showed the distribution of length of stay, which was positively skewed. This means that non-parametric tests were required to be used for analysis. Median length of stay was 3 days (1-28).

In order to analyse length of stay it was necessary to exclude all of the patients who were not admitted. The mean length of stay was compared for the different groups in each of the variables.

4.2.4.1 Length of Stay and Age

Age was investigated as a categorical variable and a continuous variable to identify any relationship with length of stay.

Kruskall-Wallis test suggested that there was no statistical difference between the age groups and length of stay ($p>0.1$). The number of patients admitted was quite different between each group, which meant that the average length of stay was affected and groups of equal size were not being compared.

Median length of stay appeared to reduce as age increased. Using age as a continuous variable gave a Spearman's correlation coefficient of -0.146 ($p=0.04$), suggesting a significant inverse correlation between age and length of stay. All groups had a wide range length of stay.

4.2.4.2 Length of Stay and Performance Status

Length of stay appeared to increase as performance status increased, with the exception of performance status 2. However only one patient in the performance status 3 group was admitted, so it was difficult to draw any conclusion. The range of length of stay was wide in all of the groups and Kruskall-Wallis confirmed that these differences were not significant (p>0.1).

4.2.4.3 Length of Stay and Intent of Treatment

Table 44. Median Length of Stay and Treatment Intent

Intent of chemotherapy	Median	N	Minimum	Maximum
Palliative	3	116	1	28
Adjuvant	2	60	1	17
Neoadjuvant	2	26	1	9
Total	3	202	1	28

Kruskall-Wallis P=0.08

Length of stay was longest in the palliative chemotherapy group and shortest in the neoadjuvant group. However, each group was a very different size and so equally sized groups could not be compared. The range of length of stay was also very wide in all groups. Kruskall-Wallis gave a borderline p-value, so it was not possible to consider this effect statistically significant (p=0.08).

4.2.4.4 Length of Stay and Disease

Skin, sarcoma and CUP groups had no patients admitted. Length of stay appeared significantly longer in the gynaecology cancer patients and shortest in the head and neck cancer patients. Kruskall-Wallis suggested that it was not possible to consider these differences statistically significant (p>0.1). Again, the groups had a wide variance and were not of equal size.

4.2.4.5 Length of Stay and Treatment

When grouped according to cytotoxicity and commissioning status, no statistically significant differences were seen in the median length of stay ($p>0.1$).

Table 45. Median Length of Stay and Treatment Grouped According to the Number of Drugs

Number of drugs	Median	N	Minimum	Maximum
1	4	57	1	24
2	2	93	1	17
3	2	49	1	28
Total	3	199	1	28

Kruskall-Wallis P=0.05

Although there was still a difference in size between the groups, this difference was less pronounced than when dividing treatment by other means. The length of stay appeared to reduce as the number of drugs increased. These differences were statistically significant according to Kruskall-Wallis. Length of stay and number of drugs had an inverse correlation with a Spearman's correlation coefficient of -0.149 ($p=0.04$).

Table 46. Median Length of Stay and Treatment Grouped According to Emetogenicity

Emetogenicity	Median	N	Minimum	Maximum
Minimal	9	1	9	9
Low	4	44	1	24
Moderate	3	85	1	28
High	2	62	1	16
Total	3	192	1	28

Kruskall-Wallis P=0.03

Again, a large variance was seen between each group. The minimally emetogenic group only had one patient in it, so comparisons could not be drawn for this group. It appeared that the more emetogenic the chemotherapy, the shorter the length of stay.

4.2.5 Summary of Primary Outcome Findings

A summary table of the main findings for the primary outcome measures was produced.

Table 47. Summary of Primary Outcome Measure Findings

	Outcome			
	Toxicity risk	**Severity (grade)**	**Admission risk**	**Length of Stay**
Predictor				
Age Categorical				
Descriptive	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)
Univariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
Multivariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
Age Continuous				
Descriptive	Not significant (p>0.1)	Kruskall- Wallis significant (p=0.03)	Not significant (p>0.1)	Negative correlation (p=0.04)
Univariable	Not significant (p>0.1)	For every year age increased, grade of toxicity reduced by 2% (p=0.04)	Not significant (p>0.1)	
Multivariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
PS				
Descriptive	Negative correlation (p<0.01)	X^2 significant (p<0.01)	X^2 significant (p<0.01)	Not significant (p>0.1)
Univariable	PS1 -26% (p<0.01)	Not significant (p>0.1)	Not significant (p>0.1)	
Multivariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
Disease				
Descriptive	X^2 significant (p<0.01)	X^2 significant (p<0.01)	X^2 significant (p<0.01)	Not significant (p>0.1)
Univariable	Breast +145% (p<0.01) Upper GI +159% (p<0.01)	Not significant (p>0.1)	Gynae +208% (p=0.02) H&N +330% (p<0.01) Upper GI +267% (p<0.01) Lung +269% (p<0.01)	
Multivariable	Breast +82% (borderline)(p=0.06) Upper GI +118% (p=0.02)	Urology +84% (p<0.01) Gynae +42% (p=0.04) Lung +73% (p<0.01)	Gynae +206% (p=0.02) H&N +408% (p<0.01) Upper GI +279% (p<0.01) Lung + 177% (p=0.03)	
Intent				
Descriptive	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)
Univariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
Multivariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
Treatment - Cytotoxicity				
Descriptive	Not significant (p>0.1)	Not significant (p>0.1)	X^2 significant (p=0.03)	Not significant (p>0.1)
Univariable	Not significant (p>0.1)	Not significant (p>0.1)	Non cyto -91% (p=0.02)	
Multivariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
Treatment - Number of Drugs				
Descriptive	Positive correlation (p<0.01)	Positive correlation (p<0.01)	X^2 significant (p<0.01)	Kruskall-Wallis borderline (p=0.05)
Univariable	2 drug -50% (p<0.01) 1 drug -59% (p<0.01)	Not significant (p>0.1)	2 drug +63% (p=0.01)	
Multivariable	2 drug -31% (borderline) (p=0.07) 1drug -50%(p<0.01)	Not significant (p>0.1)	2 drug +65% (p=0.04)	
Treatment - Commissioning				
Descriptive	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)
Univariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
Multivariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	
Treatment - Emetogenicity				
Descriptive	X^2 significant (p<0.01)	Not significant (p>0.1)	X^2 borderline (p=0.05)	Kruskall-Wallis significant (p=0.03)
Univariable	mod -29% (p=0.01) low -41% (p<0.01) min -64% (p=0.02)	Not significant (p>0.1)	Not significant (p>0.1)	
Multivariable	Not significant (p>0.1)	Not significant (p>0.1)	Not significant (p>0.1)	

4.3 Sub-Group Analyses

The three largest tumour groups were analysed as sub-populations.

There were 438 patients with breast cancer in the study population. This represented 28.5% of the population. Toxicity was reported by 186 (42.5%) breast cancer patients.

There were 329 patients with colorectal diagnoses which is 21.4% of the population studied. Toxicity was reported by 116 (35.3%) of colorectal cancer patients.

There were 242 patients with a diagnosis of lung cancer, 15.7% of the study population. Toxicity was reported by 61 (25.2%) of lung cancer patients.

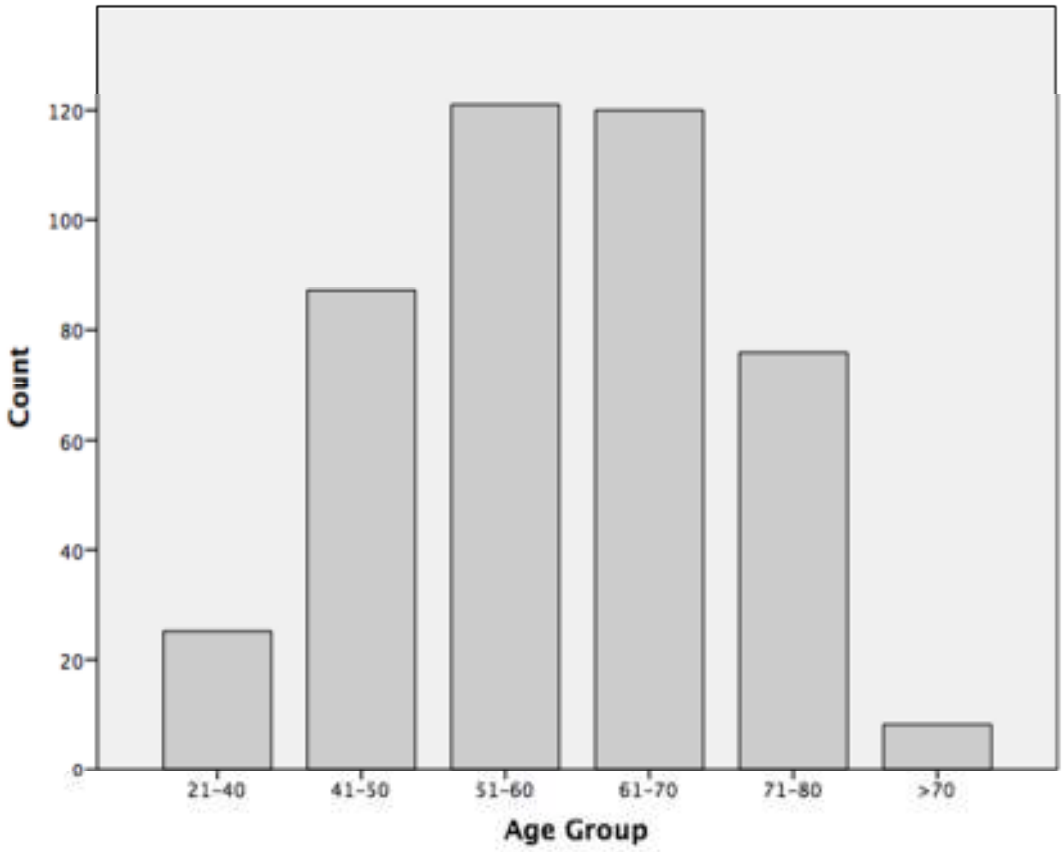


Figure 8. Distribution of Age Group in Breast cancer patients

The histogram in **figure 8** showed that the age of breast cancer patients appeared normally distributed with a peak in the aged 50-70 groups.

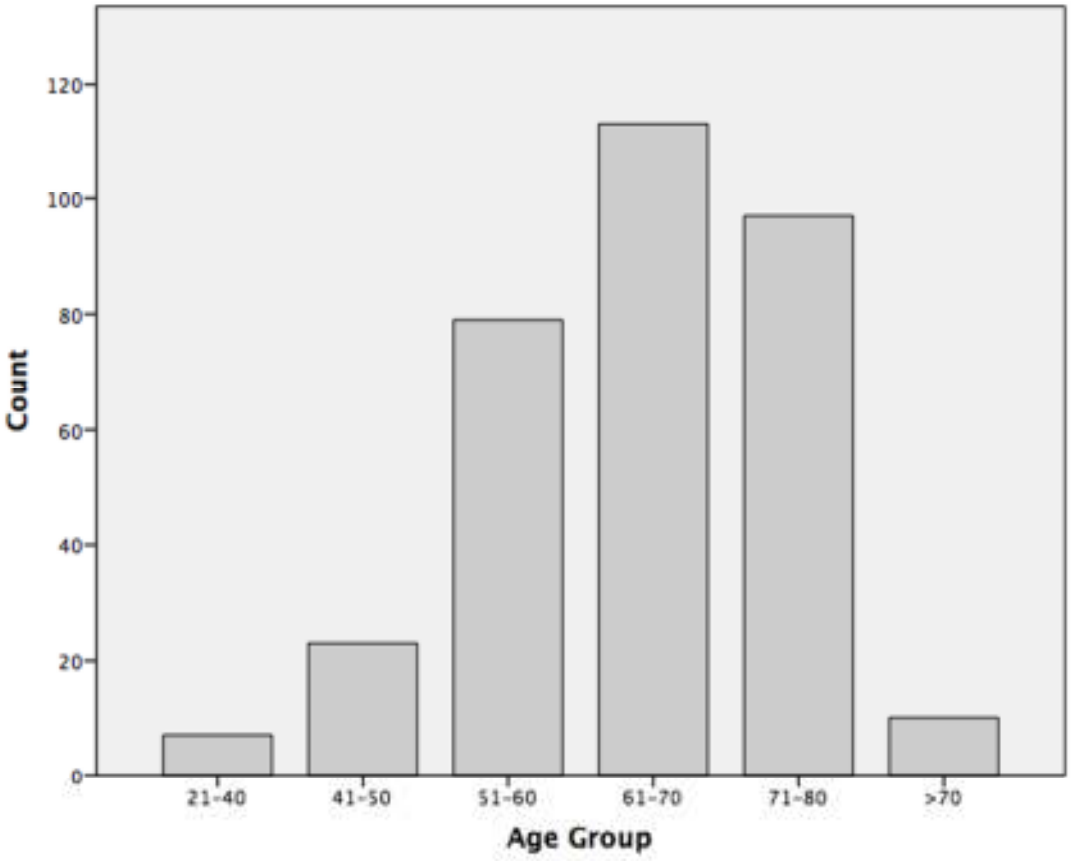


Figure 9. Distribution of Age Groups in Colorectal cancer patients

The histogram in **figure 9** had a slight negative skew and showed peak incidence in the 61-70 year old group.

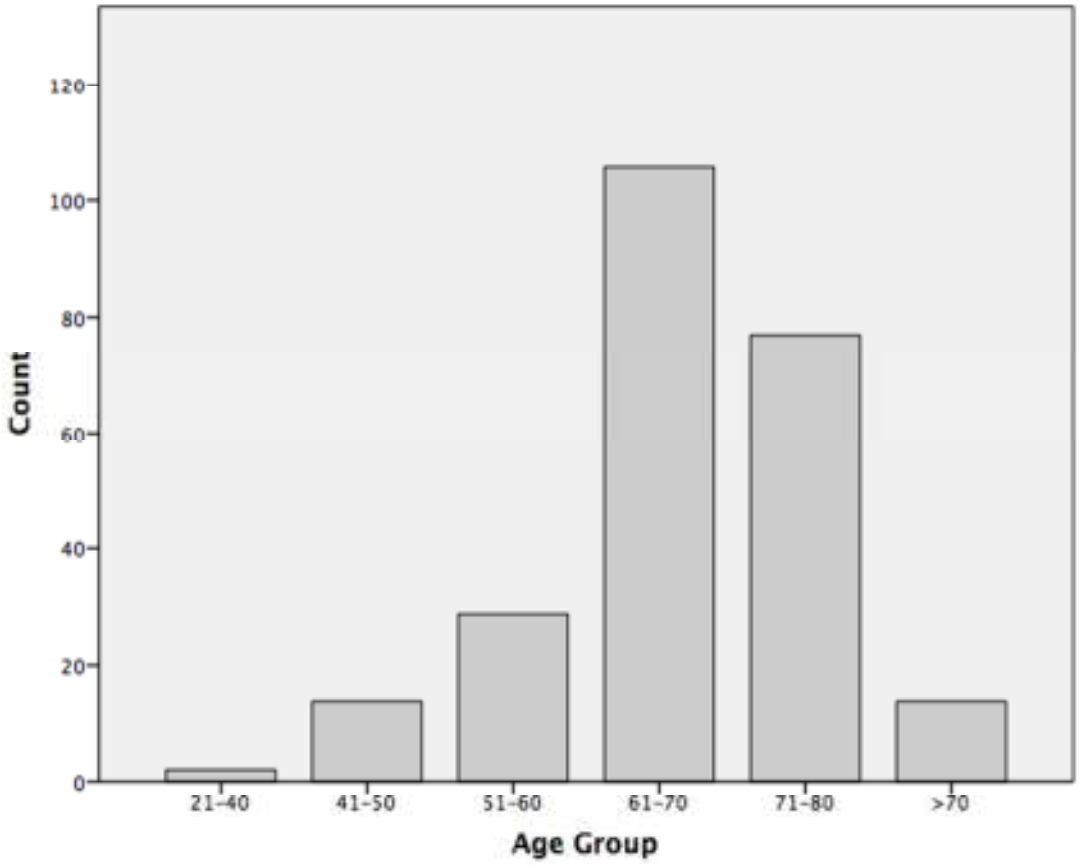


Figure 10. Age Distribution in Lung cancer patients

The histogram in **figure 10** showed a negative skew and a peak at 61-70 years.

Table 48. Distribution of Performance Status in Breast, Colorectal and Lung cancer patients

Performance Status	Breast		Colorectal		Lung		Whole Population	
	n	Valid %	n	Valid %	n	Valid %	n	Valid %
0	320	73.2	160	48.9	55	22.9	783	51.1
1	111	25.4	145	44.3	152	63.3	658	42.9
2	6	1.4	21	6.4	30	12.5	86	5.6
3			1	0.3	3	1.3	6	0.4
Total	437	100	327	100	240	100	1533	100

The majority of breast cancer patients were performance status 0. This was significantly higher than the population as a whole. The colorectal cancer patients had slightly fewer performance status 0 patients than the whole population, with lung cancer patients having the lowest percentage of performance status 0 patients. The lung group had the highest percentage of performance status 3 patients and performance status groups 1 and 2 had higher percentages of lung cancer patients compared to the whole population, which may have suggested that lung cancer patients were generally less fit than others. The data may also suggest that the breast cancer patients tended to be fitter than other disease groups.

Table 49. Distribution of Treatment Intent in Breast, Colorectal and Lung cancer patients

Treatment Intent	Breast		Colorectal		Lung		Whole Population	
	n	Valid %	n	Valid %	n	Valid %	n	Valid %
Palliative	155	35.4	177	53.8	200	82.6	833	54.2
Adjuvant	192	43.8	107	32.5	29	12	464	30.2
Neoadjuvant	91	20.8	42	12.8	13	5.4	239	15.6
	438	100	326	100	242	100	1536	100

A higher proportion of breast cancer patients received adjuvant and neoadjuvant chemotherapy than in the overall population and the other tumour groups. In the colorectal group, the distribution in the treatment intent groups was similar to that of the whole population. A significantly higher proportion of palliative chemotherapy was given in the lung group compared to 54.1% in the population as a whole.

Breast cancer patients received 25 different SACT regimens, 26 different regimens were used in the colorectal group and 20 different regimens were used in lung cancer patients.

Table 50. Distribution of Treatment Grouped by Number of Drugs in Breast, Colorectal and Lung cancer patients

Number of Drugs	Breast		Colorectal		Lung		Whole Population	
	n	Valid %	n	Valid %	n	Valid %	n	Valid %
1	126	28.8	132	43.4	26	10.7	560	37
2	34	7.8	138	45.4	209	86.4	533	35.2
3	278	63.5	34	11.2	7	2.9	420	27.8
Total	438	100	327	100	242	100	1533	100

The proportion of breast cancer patients receiving 3 drugs was significantly higher than that for the population as a whole. The colorectal cancer patients had the highest percentages of patients on 1 and 2 drugs and significantly less patients on 3 drugs than the population as a whole and less than breast cancer patients. A significantly higher proportion of lung cancer patients received a 2-drug regimen compared to the whole study population and very few patients received a triplet regimen.

Table 51. Distribution of Treatment Grouped According to Emetogenicity in Breast, Colorectal and Lung cancer patients

Emetogenicity	Breast		Colorectal		Lung		Whole Population	
	n	Valid %	n	Valid %	n	Valid %	n	Valid %
High	257	58.7	1	0.3	93	41.9	464	32
Moderate	56	12.8	142	48.3	107	48.2	544	37.5
Low	125	28.5	151	51.4	15	6.8	409	28.2
Minimal					7	2.9	33	2.3
Total	438	100	294	100	222	100	1450	100

Breast cancer patients received a significantly higher percentage of highly emetogenic chemotherapy than the population as a whole and the other tumour sites. In the colorectal group, highly emetogenic treatment was only given to one patient, making the percentage significantly lower than in the whole population. Consequently rates of moderate and low emetogenic chemotherapy were higher than in the whole population. There was a higher proportion of highly emetogenic chemotherapy used in lung cancer patients compared to the whole population and a higher proportion of moderately emetogenic chemotherapy. There were no minimally emetogenic regimens used in the 3 tumour sites of interest and only a small percentage in the whole population. .

4.3.1 Toxicity in Breast, Colorectal and Lung cancer patients

Toxicity was explored as a binary outcome variable in the tumour sites of interest using the predictors previously shown to have an association with toxicity in the whole population.

Table 52. Multivariable Logistic Regression Analysis of Toxicity in Breast cancer patients

	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
					Lower	Upper
Age (continuous)	0.009	0.009	0.299	1.009	0.992	1.027
Number of Drugs			0.048			
1	-1.205	0.498	0.016	0.3	0.113	0.796
2	-0.664	0.584	0.256	0.515	0.164	1.618
Performance Status			0.879			
0	0.339	0.904	0.708	1.404	0.239	8.258
1	0.241	0.92	0.793	1.273	0.21	7.73
Emetogenicity			0.582			
High	-0.226	0.497	0.649	0.798	0.301	2.111
Moderate	-0.424	0.409	0.299	0.654	0.294	1.458
Constant	-0.585	1.153	0.612	0.557		

Pseudo-R^2 = 0.06

Multivariable logistic regression analysis was undertaken using the same predictors shown to affect toxicity in the whole population. Only one statistically significant prediction was made by the regression analysis, and that was that patients on one drug were 70% less likely to experience a toxicity than those on 3 drugs (p=0.02).

Table 53. Multivariable Logistic Regression Analysis for Toxicity in Colorectal cancer patients

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Age (continuous)	-	0	0.012	0.996	1	0.976	1.025
Number of Drugs	-			0.727			
	1	0.426	0.54	0.431	1.531	0.531	4.414
	2	0.224	0.425	0.599	1.251	0.544	2.876
Performance Status	-			0.203			
	0	-21.22	40194	1	0	0	.
	1	-21.7	40194	1	0	0	.
	2	-22.04	40194	1	0	0	.
Emetogenicity	-			0.215			
	High	21.988	40193	1	3543630948	0	.
	Moderate	0.768	0.439	0.08	2.156	0.913	5.093
Constant		20.207	40194	1	596747124		

Pseudo-R^2=0.05

The analysis in **Table 53** also suggested that those on a moderately emetogenic regimen were 116% more likely to experience a toxicity than those on a low emetogenic chemotherapy (p=0.08), but this was of borderline significance.

A logistic regression analysis for toxicity in the lung group, using predictors previously shown to have an effect on toxicity, controlled for age, showed no statistically significant predictions (p>0.1).

4.3.2 Grade of Toxicity in Breast, Colorectal and Lung cancer patients

The severity of toxicity in the patients in the 3 largest tumour sites was explored.

Table 54. Distribution of Grade of Toxicity in Breast, Colorectal and Lung cancer patients

	Breast		Colorectal		Lung		Whole Population	
Grade of Toxicity	n	Valid %	n	Valid %	n	Valid %	n	Valid %
0	248	57.9	203	63.8	179	74.9	976	64.8
1	149	34.8	98	30.8	49	20.5	434	28.8
2	31	7.2	16	5	10	4.2	89	5.9
3			1	0.3	1	0.4	6	0.4
4							1	0.1

Pearson's χ^2= 73.69 (p<0.01)

Table 54 showed the grades of toxicities experienced by patients. The differences between the groups was statistically significant according to Pearson's χ^2 (p<0.01). There were no grade 3 or 4 toxicities experienced by breast cancer patients and the rate of grade 1 toxicity reporting was higher than the rate for the population as a whole. The grade 2 toxicity rate was also higher than the population rate. In colorectal cancer patients the percentage of patients experiencing each grade of toxicity was fairly similar to those of the population as a whole. Lower proportions of all grades of toxicity were seen in lung cancer patients compared to the whole study population and there were no grade 4 toxicities and only one grade 3. Due to the small numbers, no meaningful regression analysis could be developed for grade of toxicity. Between the three disease groups, the lung cancer patients had the highest rate of grade 0 toxicity. For each grade of toxicity, the rate was highest in breast cancer patients, followed by colorectal then lung.

4.3.3 Hospital Admission within 30 days of Chemotherapy in Breast, Colorectal and Lung cancer patients

Forty-five (10.3%) breast cancer patients were admitted within 30 days of chemotherapy. Median length of stay in breast cancer patients who were admitted was 3 days with a range of 1 to 17 days and quartiles of 1 and 6 days. The admission rate was slightly lower than that of the study population as a whole (13.1%) and median length of stay the same.

There were 32 admissions in the colorectal group and these represented 11.2% of the patients in that group. Median length of stay was 3 days, with a range of 1 to 15 and quartiles of 1 and 6.5 days which is very similar to that of the whole population.

There were 44 admissions within 30 days of chemotherapy within the lung group, accounting for 18.2% of patients, higher than the 13.1% seen in the whole study population. Median length of stay in the lung group was 2 days with a range of 1 to 14 and quartiles of 1 and 6 days, which is lower than that of the whole population (3 days).

Of the three tumour sites, lung cancer patients had the highest admission rate, which was significantly higher than that of the whole population. The lung cancer patients had the shortest length of stay, which was lower than the median of the whole population.

Logistic regression analysis of admission in the three groups using predictors previously shown to have an effect on admission, controlled for age, all failed to show any statistically significant predictions ($p>0.1$).

4.4 Individual Toxicities

The three most commonly reported toxicities were analysed.

4.4.1 Nausea

Nausea was explored as a single toxicity. Nausea was reported by 245 (15.9%) of patients

Table 55. Grade of Nausea Reported

		n	Valid %
Grade of Nausea	0	1290	84
	1	214	13.9
	2	28	1.8
	3	3	0.2
	Missing	4	
Total		1539	100

The majority of patients did not report nausea and grade 1 was the most common grade reported.

The mean age of the patients reporting nausea was 61.6 years (SD= 11.3), with a range of 24 to 90 years and quartiles of 54 and 70. The mean age of patients who did not report nausea was 63.49 years (SD= 11.4), slightly older than those patients who did report nausea. Neither value differed greatly from the mean age of the population, however Kruskall-Wallis test gave $p<0.01$, suggesting that the difference was statistically significant and nausea was seen more frequently in slightly younger patients. Nausea rate and age gave a Spearman's correlation coefficient of -0.07 ($p=0.01$) suggesting a very small inverse correlation.

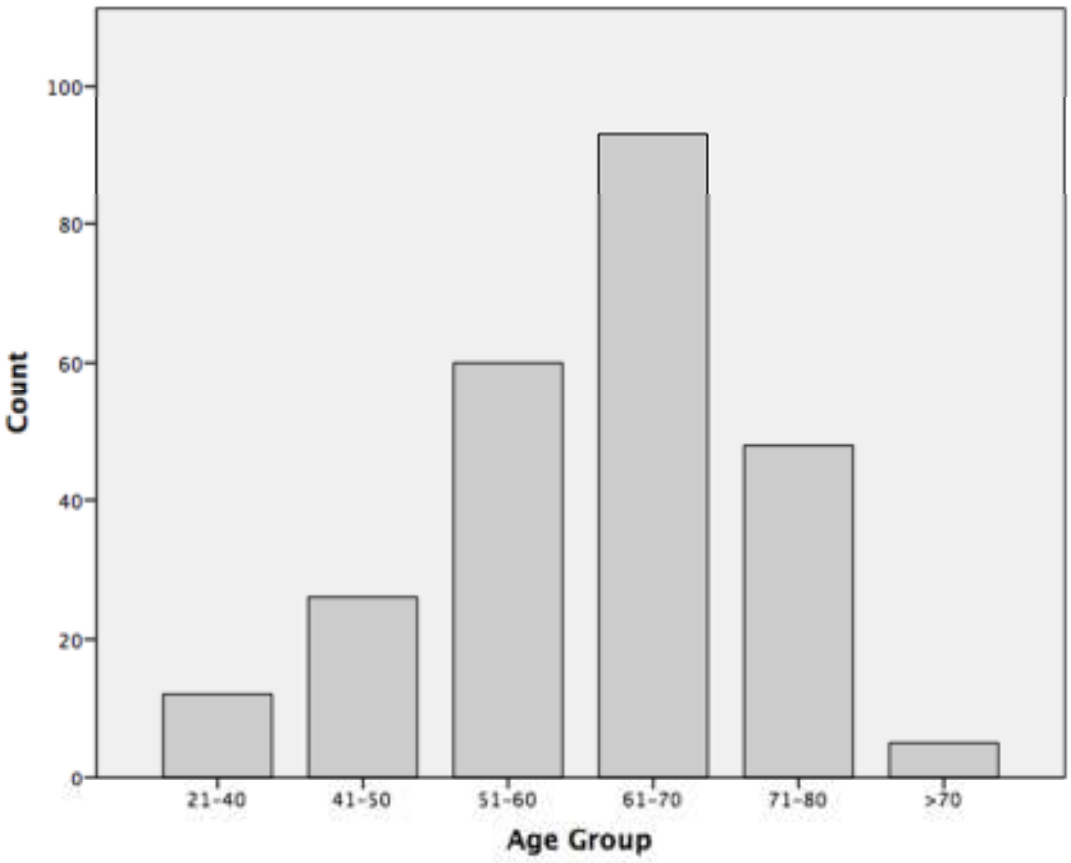


Figure 11. Distribution of Age in Patients Reporting Nausea

The histogram in **figure 11** had a near normal distribution and peaks in the age 61-70 group. This mirrored the distribution in the whole population.

When age was considered as a categorical variable, nausea did appear to be reported more by younger patients, however this was not statistically significant ($p>0.1$).

Table 56. Performance Status of Patients Reporting Nausea

		Patients Reporting Nausea	% Patients in Performance Status Group
Performance status	0	160	20.5%
	2	10	11.6%
	1	75	11.4%
Total		245	

Pearson's χ^2= 24.32 (p<0.01)

No performance status 3 or 4 patients reported nausea. The rate of nausea was highest in the performance status 0 group and appeared to reduce as performance status increases. Pearson's χ^2 suggested that this was statistically significant (p<0.01).

Table 57. Intent of Treatment in Patients Reporting Nausea

		Patients Reporting Nausea	% Patients in Intent Group
Intent of chemotherapy	Neoadjuvant	54	22.60%
	Adjuvant	89	19.30%
	Palliative	102	12.20%
Total		245	

Pearson's χ^2= 20.24 (p<0.01)

The highest rate of nausea was seen in the neoadjuvant group and lowest in those patients receiving palliative chemotherapy. Pearson's χ^2 suggested that these differences were statistically significant (p<0.01).

The rates of nausea were explored in each disease group, omitting skin, CUP and sarcoma as previously, due to the low numbers in these groups.

Table 58. Disease Groups in Patients Reporting Nausea

		Patients Reporting Nausea	% Patients in Disease Group
Disease	CNS	10	25.6%
	Breast	102	23.3%
	Upper GI	35	20.6%
	Gynaecology	19	12.6%
	Colorectal	40	12.3%
	Head&Neck	5	10.6%
	Lung	24	9.9%
	Urology	9	8.4%
	Missing	1	
Total		245	

Pearson's χ^2=39.69 (p<0.01)

The rate of nausea was highest in the CNS group and lowest in the urology cancer patients. Breast and upper GI cancer patients also had high rates of nausea, which was statistically significant (p<0.01).

Table 59. Treatment Grouped According to Cytotoxicity in Patients With Nausea

		Patients Reporting Nausea	% Patients in Treatment Group
Cytotoxicity	Cytotoxic	237	16.7%
	Mixed	7	10.6%
	Non-cytotoxic	1	2%
Total		245	

Pearson's χ^2= 9.46 (p <0.01)

Pearson's χ^2 test showed statistical significance (p<0.01), however the numbers in the groups had a wide variance, making comparison difficult.

Table 60. Treatment Grouped According to Number of Drugs in Patients With Nausea

		Patients Reporting Nausea	% Patients in Treatment Group
Number of drugs	3	119	28.4%
	2	69	13.0%
	1	51	9.1%
	Missing	6	
Total		245	

Pearson's χ^2= 71.68 (p<0.01)

Nausea appeared to be reported by more patients in the group who received 3 drugs and the rate seemed to increase as the number of drugs increased. These differences appeared to be statistically significant and there was a fairly even spread between the groups (p<0.01). Pearson's correlation coefficient was 0.18 (p<0.01), suggesting a positive correlation between nausea rate and the number of drugs.

Table 61. Treatment Grouped According to Commissioning Status in Patients With Nausea

		Patients Reporting Nausea	% Patients in Treatment Group
Commissioning Status	Baseline	237	16.6%
	CDF	8	7.5%
Total		245	

Pearson's χ^2=6.02 (p=0.01)

The rate of nausea was much higher in the baseline-commissioning group, however there was a large size difference between the two groups making comparison difficult.

Table 62. Treatment Grouped According to Emetogenicity in Patients With Nausea

		Patients Reporting Nausea	% Patients in Treatment Group
Emetogenicity	High	116	25.1%
	Moderate	74	13.6%
	Low	38	9.3%
	Minimal	1	3.0%
	Missing	16	
Total		245	

Pearson's χ^2= 48.46 (p<0.01)

The data in **Table 62** suggested that more emetogenic the chemotherapy the higher the rate of nausea.

Table 63. Multivariable Logistic Regression of Nausea

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Age (continuous)		-0.001	0.007	0.905	0.999	0.986	1.012
Number of drugs				0			
	1	-1.233	0.289	0	0.292	0.165	0.514
	2	-1.056	0.238	0	0.348	0.218	0.555
Performance Status				0.15			
	0	19.201	16115	0.999	2.18E+08	0	.
	1	18.799	16115	0.999	1.46E+08	0	.
	2	18.989	16115	0.999	1.77E+08	0	.
Emetogenicity				0.916			
	High	-0.208	1.616	0.897	0.812	0.034	19.289
	Moderate	-0.138	1.604	0.932	0.872	0.038	20.213
	Low	-0.315	1.591	0.843	0.73	0.032	16.494
Treatment Intent				0.895			
	Palliative	-0.009	0.235	0.968	0.991	0.625	1.571
	Adjuvant	0.073	0.211	0.731	1.075	0.711	1.626
Commissioning Status							
	Baseline	0.054	0.589	0.927	1.055	0.332	3.35
Cytotoxicity				0.163			
	Cytotoxic	1.085	0.618	0.079	2.959	0.881	9.943
	Non-Cytotoxic	-0.599	1.631	0.713	0.549	0.022	13.441
Constant		-20.82	16115	0.999	0		

Pseudo R^2 = 0.06

The Pseudo R^2 in the logistic regression shown in **Table 63** was relatively small, suggesting that the analysis explained a small amount of the variance in nausea. The analysis showed the following significant predictions for the number of drugs:

- Patients on 1 drug were 71% less likely to experience nausea than those on 3 drugs ($p<0.01$)
- Patients on 2 drugs were 65% less likely to experience nausea than those on 3 drugs ($p<0.01$)

The prediction for cytotoxicity appeared to be borderline significant (p=0.08), but due to the differences in the sizes of the groups, a relationship could not be reliably shown.

4.4.1.1 Grade of Nausea

There were no statistically significant differences between the age groups experiencing each grade of nausea, although the groups were not of a similar size (p>0.1). Performance status did not seem to affect the grade of nausea, with no significant difference (p>0.1), nor did intent of treatment or disease (p>0.1).

When looking at treatment, none of the methods of grouping treatments showed any statistically significant difference in the rates of each grade of nausea (p>0.1). Group sizes were not equal and many groups had few of no patients in them. As no statistically significant relationships were identified in the descriptive statistics, regression analysis was not performed for grade of nausea.

4.4.1.2 Nausea and Admission

The number of patients who reported nausea, who were admitted within 30 days of chemotherapy was 34 (13.9%). Patients who did not report nausea had an admission rate of 13%. This was very similar to the admission rate for the population as a whole, the patients reporting nausea had a median length of stay of 2 days (1-28), which was lower than the median for the entire study population (3 days [1-28]). Those not reporting nausea had a median length of stay of 3 days (1-28). No statistically significant predictions were found in a logistic regression analysis for admission rates (p>0.1).

4.4.2 Vomiting

Vomiting was investigated in the same way as nausea. Vomiting was reported by 89 (5.8%) of patients.

Table 64. Grade of Vomiting

		n	Valid %
Grade of Vomiting	0	1446	94.2
	1	52	3.4
	2	35	2.3
	3	2	0.1
	Total	1535	100
	Missing	4	
Total		1539	

Grade 1 was the most frequently reported grade of vomiting with only 2 patients reporting grade 3 and no grade 4 vomiting being reported.

The mean age of those patients reporting vomiting was 59.5 years (SD= 13.2), with a range of 24 to 83 years and quartiles of 50.5 and 70 years. The mean age of those not reporting vomiting was 63.41 years (SD=11.2), which was almost identical to that of the whole population. Kruskall-Wallis gave p=0.01, suggesting that this difference was statistically significant and vomiting was seen in slightly younger patients.

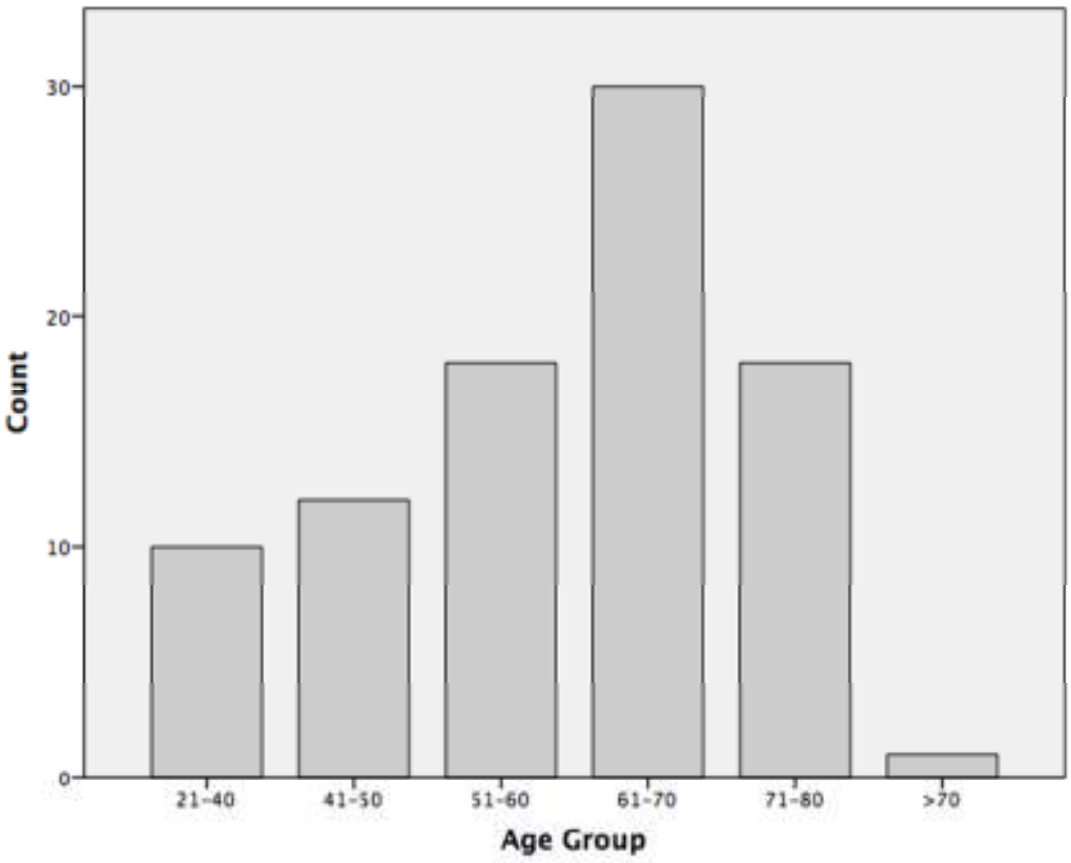


Figure 12. Distribution of Age in Patients Experiencing Vomiting

The histogram in **figure 12** showed that there is a peak incidence at 61-70 years. This was the same as the whole population and the same as nausea.

Table 65. Distribution of Age in Patients Reporting Vomiting

		Number Experiencing Vomiting	% Patients in Age Group
Age group (years)	21-40	10	16.4%
	41-50	12	7.5%
	51-60	18	5.5%
	61-70	30	5.5%
	71-80	18	4.6%
	>70	1	1.9%
Total		89	

Pearson's χ^2=15.99 (p<0.01)

The rate of vomiting appeared to decrease as age increased. Spearman's correlation coefficient for age and vomiting is -0.081 (p=0.02) suggesting an inverse correlation.

No statistically significant relationship was seen between performance status and vomiting (p>0.1).

Table 66. Intent of Chemotherapy in Patients Reporting Vomiting

		Number Experiencing Vomiting	% Patients in Intent Group
Intent of chemotherapy	Neoadjuvant	23	9.6%
	Palliative	45	5.4%
	Adjuvant	21	4.6%
Total		89	

Pearson's χ^2=7.92 (p=0.02)

When intent of treatment was explored, neoadjuvant patients had the highest rate of vomiting and the lowest rate was seen in patients receiving adjuvant

treatment. The differences were not large but were statistically significant (p>0.1).

Table 67. Disease in Patients Reporting Vomiting

		Number Experiencing Vomiting	% Patients in Disease Group
Disease	CNS	6	15.4%
	Upper GI	16	9.5%
	Breast	35	8.0%
	Gynaecology	7	4.6%
	Head&Neck	2	4.3%
	Colorectal	11	3.4%
	Lung	7	2.9%
	Urology	3	2.8%
	Missing	2	
Total		89	

Pearson's χ^2=24.63 (p<0.01)

The rate of vomiting was significantly higher in the breast and CNS groups. The differences between the groups appeared to be statistically significant (p<0.01).

The rate of vomiting by treatment grouped according to cytotoxicity showed that there was a wide variance in the size of the groups, making comparison difficult.

Table 68. Treatment Grouped According to Number of Drugs in Patients Reporting Vomiting

		Number Experiencing Vomiting	% Patients in Treatment Group
Number of Drugs	3	51	12.2%
	2	28	5.3%
	1	9	1.6%
	Missing	1	
Total		89	

Pearson's χ^2=49.6 (p<0.01)

It appeared that the more drugs given, the higher the rate of vomiting. Pearson's correlation coefficient was 0.184 (p<0.01) suggesting a positive correlation.

The rate of vomiting by treatment grouped according to commissioning status showed that there was a large variance in the size of the groups making comparison difficult.

Table 69. Treatment Grouped According to Emetogenicity in Patients Reporting Vomiting

		Number Experiencing Vomiting	% Patients in Treatment Group
Emetogenicity	High	48	10.4%
	Moderate	29	5.4%
	Low	7	1.70%
	Minimal	0	0%
	Missing	5	
Total		89	

Pearson's χ^2=32.51 (p<0.01)

As with nausea, the data in **Table 69** suggested that the more emetogenic a treatment, the higher the rate of vomiting.

Table 70. Multivariable Logistic Regression Analysis for Vomiting

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Age (continuous)		-0.01	0.011	0.335	0.99	0.969	1.011
Treatment Intent				0.02			
	Palliative	0.501	0.36	0.164	1.651	0.815	3.346
	Adjuvant	-0.447	0.349	0.2	0.639	0.323	1.268
Disease				0.123			
	CNS	1.832	1.192	0.124	6.245	0.604	64.582
	Breast	0.923	1.094	0.399	2.516	0.295	21.481
	Colorectal	0.44	1.075	0.682	1.553	0.189	12.773
	Gynaecology	0.724	1.097	0.51	2.062	0.24	17.702
	Head & Neck	1.452	1.356	0.284	4.272	0.3	60.88
	Upper GI	1.06	1.083	0.327	2.887	0.346	24.09
	Lung	-0.52	1.124	0.644	0.595	0.066	5.382
Number of Drugs				0.034			
	1	-1.384	0.542	0.011	0.251	0.087	0.726
	2	-0.207	0.409	0.613	0.813	0.365	1.814
Emetogenicity				0.235			
	High	17.498	7103.916	0.998	39751906	0	.
	Moderate	17.04	7103.916	0.998	25139573	0	.
	Low	16.229	7103.916	0.998	11171231	0	.
Constant		-19.705	7103.916	0.998	0		

Pseudo R^2=0.05

A logistic regression analysis for vomiting, using predictors shown to have a relationship by descriptive statistics, controlled for age showed that the only statistically significant prediction is with the number of drugs. The analysis suggested that patients who received 1 drug were 75% less likely to experience vomiting than those on 3 drugs (p=0.01).

4.4.2.1 Grade of Vomiting

The only statistically significant relationship shown by the descriptive statistics was that between age and grade of vomiting ($p<0.01$), however this did not yield a statistically significant correlation coefficient ($p>0.1$). Regression analysis was therefore not undertaken.

4.4.2.2 Vomiting and Admission Within 30 Days of Chemotherapy

Of the patients who reported vomiting, 14 (15.7%), were admitted within 30 days of chemotherapy, which was slightly higher than the rate for the whole study population. The patients who did not report vomiting had an admission rate of 13%. Pearson's χ^2 did not show this difference to be statistically significant ($p>0.1$). The median length of stay in patients reporting vomiting was 1.5 days (1-8), compared to 3 days (1-28) in those not reporting vomiting. No statistically significant predictions were found in a logistic regression analysis ($p>0.1$).

4.4.3 Fatigue

Fatigue was explored in a similar way to nausea and vomiting. Fatigue was the third most reported toxicity and was reported by 159 (10.3%) of patients.

Table 71. Grade of Fatigue

		n	Valid %
Grade of Fatigue	0	1375	89.6
	1	151	9.8
	2	8	0.5
	Total	1534	100
	Missing	5	
Total		1539	

The mean age of patients reporting fatigue was 63.1 years (SD=10.4), with a range of 38 to 82 and quartiles of 53.25 and 73.5. This compared to a mean of 63.2 years (SD= 11.5) for patients not reporting fatigue and the same for the population as a whole. Clearly there was no difference in these values.

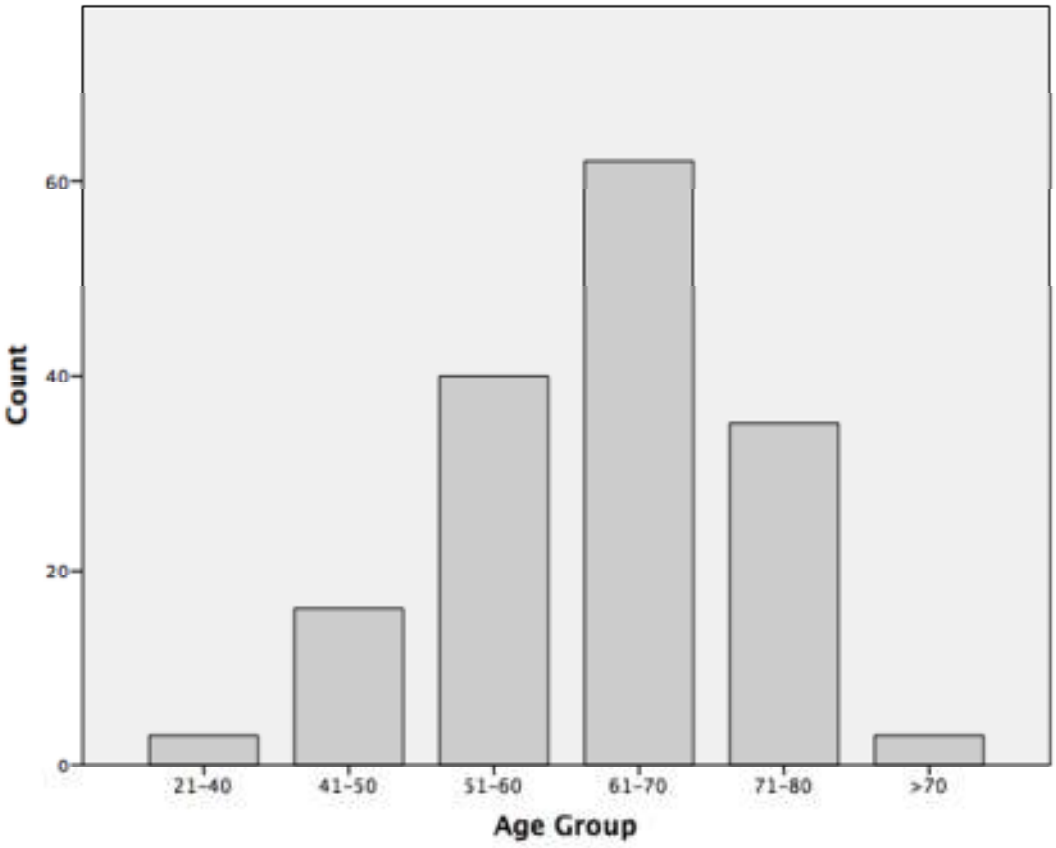


Figure 13. Distribution of Age in Patients Reporting Fatigue

The distribution of age in patients reporting fatigue followed a similar pattern to that of the whole population and the other toxicities. There was a peak incidence at 61-70 years.

When treated as a categorical variable, the differences between the age groups was shown to be not statistically significant ($p>0.1$). Performance status and treatment intent appeared to have no relationship with fatigue either.

Table 72. Disease in Patients Reporting Fatigue

		Number Reporting Fatigue	% Patients in Disease Group
Disease	Breast	62	14.2%
	Gynaecology	18	11.9%
	Upper GI	20	11.8%
	Urology	11	10.3%
	Head&Neck	4	8.5%
	CNS	3	7.7%
	Colorectal	24	7.4%
	Lung	17	7.0%
Total		159	

Pearson's χ^2=14.05 (p=0.05)

Breast cancer patients reported the highest rate of fatigue, closely followed by gynaecology and Upper GI cancer patients with lung cancer patients reporting the lowest rate.

Table 73. Treatment Grouped According to Cytotoxicity in Patients Reporting Fatigue.

		Number Reporting Fatigue	% Patients in Treatment Group
Cytotoxicity	Mixed	18	27.3%
	Cytotoxic	138	9.7%
	Non-cytotoxic	3	5.9%
Total		159	

Pearson's χ^2= 22 (p<0.01)

Those receiving a mixed regimen of a cytotoxic and non-cytotoxic drug had a much higher rate of fatigue. Although this appeared to be statistically significant (p<0.01), the sizes of the groups was very uneven, making comparison difficult.

Table 74. Treatment Grouped According to the Number of Drugs in Patients Reporting Fatigue

		Number Reporting Fatigue	% Patients in Treatment Group
Number of Drugs	3	62	14.8%
	1	48	8.6%
	2	46	8.6%
	Missing	3	
Total		159	

Pearson's χ^2=11.56 (p<0.01)

Those receiving 3 drugs had a much higher rate of reporting than the other two groups, which had the same rate of fatigue. This difference was statistically significant (p<0.01).

Table 75. Treatment Grouped According to Commissioning Status in Patients Reporting Fatigue

		Number Reporting Fatigue	% Patients in Treatment Group
Commissioning Status	CDF	21	19.8%
	Baseline	138	9.7%
Total		159	

Pearson's χ^2=10.92 (p<0.01)

Those on CDF drugs had a significantly higher rate of fatigue than those on baseline commissioned drugs. It should be noted that the baseline group was significantly larger than the CDF group, which made comparisons less reliable.

No statistically significant difference between the groups was found, when treatments were grouped according to emetogenicity (p>0.1).

Table 76. Multivariable Logistic Regression for Fatigue

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Age (continuous)		0.008	0.008	0.33	1.008	0.992	1.024
Number of Drugs				0.098			
	1	-0.522	0.242	0.031	0.593	0.369	0.954
	2	-0.325	0.273	0.233	0.723	0.423	1.233
Disease				0.336			
	CNS	-0.307	0.7	0.661	0.735	0.187	2.899
	Breast	0.164	0.387	0.671	1.178	0.552	2.514
	Colorectal	-0.468	0.394	0.236	0.626	0.289	1.357
	Gynaecology	0.179	0.408	0.661	1.196	0.537	2.663
	Head&Neck	-0.07	0.626	0.911	0.932	0.273	3.179
	Upper GI	-0.043	0.416	0.917	0.958	0.424	2.164
	Lung	-0.509	0.422	0.228	0.601	0.263	1.375
Constant		-2.272	0.663	0.001	0.103		

Pseudo-R^2=0.01

The analysis in **Table 76** omitted treatment grouped according to commissioning status and cytotoxicity due to the uneven sizes, meaning that reliable conclusions were unlikely to be drawn. The analysis had a very small pseudo-R^2 value, suggesting that it only explained a very small amount of the variance in fatigue. It suggested that those patients who received 1 drug were 41% less likely to experience fatigue, compared to those who received 3 drugs (p=0.03). No other statistically significant relationships were shown in the analysis (p>0.1). This could suggest type 1 error with the descriptive statistics.

4.4.3.1 Grade of Fatigue

Descriptive statistics suggested that age group, performance status, treatment intent and treatment grouped according to commissioning status all had statistically significant relationships with the severity of fatigue ($p<0.05$). However the number of patients in each group was small, due to the numbers of patients reporting fatigue. This made showing relationships difficult. No statistically significant predictions were seen in an ordinal regression analysis of fatigue grade using the above predictors that had shown a relationship with fatigue in the descriptive statistics ($p>0.1$).

4.4.3.2 Fatigue and Admission

Of the patients reporting fatigue, 26 (16.4%) were admitted within 30 days of chemotherapy. This was higher than the percentage admitted for the whole study population (13.1%) and higher than the rate for patients not reporting fatigue (12.8%). However, Pearson's χ^2 test suggested that this difference was not statistically significant ($p>0.1$). Median length of stay in patients reporting fatigue was 2.5 days (1-11), which was less than the median for those patients not reporting fatigue of 3 days (1-28). The median length of stay for the population as a whole was 3 days (1-28). The length of stay of those patients reporting fatigue had a range of 1 to 11 and quartiles of 1 and 6. The number admitted was too small to perform any meaningful regression analysis.

5.0 Discussion

Following a thorough literature search, which found various studies alluding to predictors of chemotherapy toxicity, this research set out to identify the predictors of chemotherapy toxicity, severity of toxicity, hospital admission due to toxicity and subsequent length of stay, as well as the sub-group analyses and secondary outcome measures alluded to in the aims and objectives in **Section 2.0**

The data enabled an overall incidence of chemotherapy toxicity and admission to be established and the following key findings were seen as the research answered the questions posed by the aim and objectives described:

Primary Outcome Measures

- Toxicity
    - Negative correlation between performance status and toxicity rate ($p<0.01$) and univariable analysis suggested that PS1 patients had a lower risk of toxicity than PS0 patients ($p<0.01$)
    - Breast ($p=0.06$) and upper GI cancer patients ($p=0.02$) had a higher risk of toxicity than urology patients
    - The higher the number of drugs, the higher the rate of toxicity ($p<0.01$)
    - In the univariable analysis, the more emetogenic a chemotherapy treatment, the higher the rate of toxicity ([Moderate $p=0.02$], [low $p<0.01$], [minimal $p=0.02$])
- Severity of Toxicity
    - In univariable analysis, as age increased, the severity of toxicity reduced ($p=0.04$)
    - Urology ($p<0.01$), gynaecology ($p=0.04$) and lung cancer patients ($p<0.01$) experienced higher grades of toxicity than breast cancer patients
    - Positive correlation between the number of drugs and the severity of toxicity but not confirmed in regression analysis ($p<0.01$)
- Hospital Admission
    - Gynaecology ($p=0.02$), head and neck ($p<0.01$), upper GI ($p<0.01$) and lung cancer patients ($p=0.03$) had a higher risk of hospital admission than urology patients
    - Non-cytotoxic chemotherapy carried a lower risk of admission then cytotoxic in the univariable regression ($p=0.02$)
    - A regimen containing 2 drugs had a higher risk of admission than a regimen containing 1 drug ($p=0.04$)
- Length of Stay
    - There was a negative correlation between age and length of stay ($p=0.04$)
    - Median length of stay reduced as the number of drugs in a regimen increased ($p=0.05$)

- The more emetogenic a regimen, the lower the length of stay (p=0.03)

Breast Cancer Patients

- Patients on 1 drug less likely to experience a toxicity than those on 3 drugs (p=0.02)

Colorectal Cancer Patients

- Patients on moderately emetogenic chemotherapy more likely to experience toxicity than those on low emetogenic risk chemotherapy (p=0.08 borderline)

Nausea

- The higher the number of drugs, the more likely patients were to report nausea ([1 drug p<0.01], [2 drug p<0.01])

Vomiting

- Patients on 1 drugs less likely to report vomiting than those on 3 drugs (p=0.01)

Fatigue

- Patients on 1 drug less likely to experience toxicity than those on 3 drugs (p=0.03)

5.1 Population

This study looked at the population of patients receiving chemotherapy or anticancer therapy in a large, UK inner city teaching hospital. Almost the entire population of oncology patients was included in the study, with the exclusions as mentioned in the methodology. Toxicity was investigated as a binary variable where all toxicities were combined, along with severity of toxicity, admissions and length of stay. No other study was found that involved a similar population, investigating similar outcomes. National data was available on the administration of SACT, but patient level detail was not published, nor was analysis of the population receiving the chemotherapy, although this data was submitted on a monthly basis as mandated by NHS England (Public Health England, 2018). As such, comparison of the entire dataset was not possible, however when individual outcomes were considered, it was possible to compare these to published studies in some cases.

With incomplete entries being excluded, 1539 patients were included in the study population. This was a large population that allowed for robust data analysis. The population was heterogeneous in terms of age, diagnosis, performance status and treatment received. The age of the population had a negatively skewed distribution that would be expected of a large population and the average age was 65 years old. Cancer Research UK statistics suggested that the highest incidence of cancer was in patients over 75 years old (Cancer Research UK, 2015e). The number of new cases peaks in the 65-70 year old patients. Cancer incidence and number of patients receiving chemotherapy does not necessarily correlate as many people with cancer do not receive chemotherapy. There was no national data available on the average age of people receiving chemotherapy. The distribution of age, did however, relate to the known incidence of cancer nationally.

The majority of patients were performance status 0 or 1. Only 92 (6%) of the patients receiving chemotherapy had a performance status of 2 or above and 3 was the highest performance status recorded for the population. This was as

would be expected, as national recommendations suggest that chemotherapy should only be used in patients with performance status 3 or 4 with caution and after discussion with the MDT (Mort *et al*., 2008). The rationale for this is that chemotherapy carries risk and is associated with significant morbidity and giving chemotherapy to less fit patients can result in higher rates of mortality. No similar studies were found that reported distribution of performance status in a chemotherapy population.

A wide variety of cancer diagnoses were included in the population. Breast, colorectal and lung cancers accounted for the largest groups of patients, which related to UK cancer statistics that suggested that breast, prostate, lung and bowel cancers accounted for over half of cancers diagnosed in the UK in 2015 (Cancer Research UK, 2015e). Prostate cancer patients only made up 3.6% (55 patients) of the study population, however, at the time of writing, SACT was only used in metastatic prostate cancer at NUH, in line with international guidance (Horwich *et al*., 2010). Advanced prostate cancer accounted for 40% of prostate cancer diagnoses in England in 2015, and not all of these patients would receive treatment, hence the lower numbers of prostate cancer patients in the study population (Cancer Research UK. 2015e). Central nervous system, cancer of unknown primary, primary peritoneum, vaginal, nasopharynx, tongue, hypopharynx, larynx, floor of mouth, hepatocellular, and gastro-oesophageal junction cancers had very low numbers and this reflected the rarity of the diseases and potential for other treatment modalities. Sarcomas and germ cell tumours had low numbers as there was a high likelihood that these patients received their chemotherapy on an inpatient basis and were excluded from the call back service. Renal cell and melanoma also had small numbers as these patients received their call back from a clinical nurse specialist who did not record the toxicity assessment in the database. In order to facilitate meaningful data analysis, the diseases were grouped according to the multi-disciplinary team to which they pertained. This mirrored clinical practice, as at NUH, as in most centres, clinicians tended to specialise in treating cancers of one of two types, usually grouped by body systems. This was the practice nationally (Department of Health, 2011), with peer review being centred around the specialist MDT.

Just over half of the treatments given had a palliative intent. According to cancer research UK, 28% of patients with cancer in the UK in 2013/14, received chemotherapy with a curative or palliative intent (Cancer Research UK, 2015d). Little data could be found on national trends in intent of treatment, so comparison of these figures was not possible. The SACT website did give a report on the top regimens by diagnostic groups. For breast cancer, the regimens were broken up into treatment intent, where slightly more cycles of chemotherapy were of palliative intent than of curative intent (Chemotherapy Intelligence Unit, 2015). In the national data in colorectal cancer patients, over four times as many palliative cycles of chemotherapy were given compared to curative. The other tumour sites were not broken down into intent of chemotherapy, however breast and colorectal were probably the two largest groups where chemotherapy of adjuvant or neoadjuvant intent was used. It was likely that treatment intent was affected by a number of other variables such as age, treatment and performance status. Age and performance status were likely to be taken into consideration when deciding if a patient was fit enough for chemotherapy and adjuvant and neoadjuvant treatments were likely to be more intensive, so these variables would play an important role in the decision process. Treatment was interlinked with intent as treatments were often only used for one treatment intent in a particular disease, however there could have been overlaps such as FEC, which was used in palliative, neoadjuvant and adjuvant settings at NUH. Doses of drugs used across differing treatment intents may have been different.

A significantly higher percentage of adjuvant and neoadjuvant patients were performance status 0 than in the palliative group, which suggested that these patients were fitter. This could potentially have a significant impact on the occurrence and severity of toxicity, and highlighted the interaction between treatment intent and performance status.

A wide variety of different treatments were used in the study population. The number of patients receiving each type of treatment reflected the numbers of patients with each cancer diagnosis. For example, breast cancer was the largest disease group accounting for 28.5% (439 patients) of the study population and the most commonly used regimen was FEC75 used in 242 (15.7%) patients. This mirrored the national picture of FEC being the most commonly used chemotherapy regimen (Chemotherapy Intelligence Unit, 2015). It was necessary to group the treatments in order to produce meaningful data analysis. Several methods of grouping were explored that reflected the clinical relevance of the treatments. Targeted treatments account for an increasing number of anticancer agents and as such, treatments were grouped according to cytotoxicity, as most targeted therapies are not considered cytotoxic. A significantly higher proportion of patients received cytotoxic chemotherapy (92.4% [1422 patients]) compared to those who received non-cytotoxic or mixed treatment. This made comparison of the groups very difficult, as the numbers in the smaller groups were very small and it was not possible to rule out size effect. This method of categorisation had little meaning for clinical practice, as it was too broad to make any meaningful conclusions.

Treatment was also grouped according to the number of drugs in the regimen, which ranged between one and three and the spread amongst the groups was fairly even. This method of grouping was employed as it was suspected that the more drugs used, the higher the level of toxicity due to the potential additive effects of different agents.

Commissioning of chemotherapy was highly relevant to current clinical practice and as such treatments were grouped according to commissioning status. The cancer drugs fund remains a controversial means of funding chemotherapy, with much focus on the outcomes of treatments. Indeed in 2017, an analysis of outcomes of patients who received drugs funded by the cancer drugs fund, found that only 18 (38%) of treatments reported a statistically significant overall survival advantage with a median of 3.1 months (1.4-15.7) (Aggarwal *et al*.,

2017). An expenditure of £1.3billon was seen from the launch of the cancer drugs fund until it was rationalised back into NICE in 2016. The authors concluded that the cancer drugs fund was not an effective use of money and that there was no evidence found to support a drug only ring-fenced fund. No reports of toxicity of drugs funded by the cancer drugs fund have been published and as such, toxicity may be a factor of interest when discussing the benefits of the cancer drugs fund. No hypothesis could be formed on the occurrence of toxicity in these groups and it was accepted that commissioning status could not have an effect on toxicity and this method of grouping was merely observational. Unfortunately the size of the groups was very uneven with 1431 (93%) of patients receiving baseline commissioned chemotherapy. This made comparison between the groups very difficult as size effect was very likely.

Drugs are organised by class in the BNF (Baxter, 2018). Different drug classes are often associated with different toxicities and so it was decided to group treatments according to drug class. There are 10 classes in the BNF and these were employed for the grouping, however this produced groups of very uneven size, with the most common group accounting for 526 (34.2%) of patients with the smallest accounting for just 2 patients (0.1%). When dividing the treatment regimens into drug class, it was not possible to encompass all of the drug classes in the combination regimens as this would have resulted in too many variables to allow for robust data analysis. As such, only the first category into which a combination regimen falls was used. Drug class showed signs of having some effect on the prediction of toxicity, but to fully and accurately explore this effect, it would be necessary to use a much larger population to allow for more groups in data analysis and a robust means of classifying the treatments would be imperative. Drug class was omitted from further analysis.

The emetogenic potential of chemotherapy agents is highly relevant in clinical practice. Local, national and international guidelines exist and guide antiemetic therapy for both treatment and prevention of chemotherapy induced nausea and vomiting (Hesketh *et al.,* 2017a). Given the relevance and potential impact

on practice, treatments were grouped according to emetogenicity, in accordance with American Society of Clinical Oncology (ASCO) guidelines. Similar numbers of patients were seen in the high, moderate and low groups, with the minimal group only accounting for 2.1% (32 patients) of the population. This meant that meaningful conclusions were unlikely to be drawn from the data.

5.2 Toxicity Incidence

One of the main aims of this research was to establish an overall incidence of toxicity for a chemotherapy population. In the study, 542 (35.6%) of patients experienced a toxicity of any grade. No data reporting overall incidence of toxicity in a similar population was found. It is common for clinical trials to report toxicity rates by grade, but this is for specific drugs in specific indications so comparison to this population could not be made. This was, of course, a crude measure and could be used for descriptive purposes only as the effect or severity of those toxicities was not explained by this figure.

Only one grade 4 toxicity was reported, and the most common grade of toxicity was grade 1. Nausea, vomiting and fatigue were the most commonly reported toxicities and nausea had the highest mean grade. These individual toxicities were explored later in the sub-group analyses. Fever was reported by a low percentage of patients but was not included in this analysis as it was not recorded as a graded toxicity. For the majority of regimens, the neutrophil count was unlikely to drop until at least a week after chemotherapy and as such it would not be anticipated that any chemotherapy-associated fevers would be seen so soon after chemotherapy as when the toxicity assessment took place (Brooks *et al*., 2012).

Extravasation was reported by only three people. It was decided not to explore this within this study as extravasation was usually reported and managed whilst undergoing chemotherapy. It is likely that these three patients had an extravasation whilst undergoing chemotherapy and this was managed by the nursing staff in line with local policy and guidelines. Grade of extravasation was not reported and so comparison to other toxicities would not be possible. In order to explore extravasation further, a different data collection method would be required, which was beyond the remit of this study.

5.3 Primary Outcome Measures

5.3.1 Toxicity

The first primary outcome to be explored was the occurrence of toxicity as a binary variable. This variable was used to give an overall incidence of toxicity for the whole population as described above. The various predictors were explored to identify any effect on the occurrence of toxicity.

5.3.1.1 Toxicity and Age

There was no difference in the mean age of those patients experiencing toxicity and those who did not experience toxicity. When age was grouped into a categorical variable, there was no apparent difference between the groups. The age group 51-60 year olds reported the most toxicities, and the over 80 years old group reported the least, however these differences were not statistically significant ($p>0.1$). From a logistical regression analysis, it appeared that age was not associated with the occurrence of toxicity. No literature was found to associate age with the overall occurrence of toxicity, however Balducci and Extermann suggested a number of toxicities that increase with age (Balducci and Extermann, 2000), however much of this was based upon theory of the mechanisms that cause toxicity, rather than data from large scale clinical studies. The findings of this study were not able to draw any conclusions around the association of age with toxicity occurrence and certainly could not suggest that age is a predictor of toxicity.

Hurria *et al.* claimed that the risk of toxicity increases with age (Hurria *et al*., 2011). This was a large study with a heterogeneous population of older adults in several centres with several different types of cancer. It identified being aged over 72 years as a risk factor for chemotherapy toxicity. It was not possible to corroborate this claim with the data from this study. Similarly Balducci and Extermann's claimed that increasing age increases the incidence of toxicity could not be confirmed by this study (Balducci and Extermann, 2000).

It was expected that as co-morbidity tends to increase with age, that toxicity may also increase, but this was not the case. The toxicities recorded in this study relied on patient reporting during a telephone consultation and so there could have been a number of other factors that influenced this, of which age may have been a part, but elucidating these factors was beyond the remit of this study.

5.3.1.2 Toxicity and Performance Status

Performance status is an important tool used regularly in clinical practice and can be used to influence the decision of whether or not to treat a patient with chemotherapy (Mort *et al*., 2008). It was therefore important to ascertain any effect of performance status on the occurrence of toxicity. The rate of toxicity reporting appeared to reduce as performance status increased. Only 6% (90 patients) of the population were performance status 2 or 3 and as such it was difficult to draw any conclusions for these groups. However the correlation coefficient of -0.082 ($p<0.01$) between rate of toxicity and performance status suggested a slight inverse correlation.

Logistic regression analysis showed that performance status did appear to be a significant predictor of toxicity when treated as an independent variable. The analysis produced had a low pseudo R^2 value suggesting that it explained only a minimal amount of variance in toxicity, however there were some statistically significant predictions. The analysis suggested that patients with performance status 1 were 26% less likely to experience a toxicity than those who were performance status 0 ($p<0.01$). There was a similar effect seen in performance status 2 patients but this was of borderline significance ($p=0.06$). In the study population, the majority of patients were performance status 0 or 1 and only 86 (5.6%) were performance status 2, giving a selection bias and making drawing conclusions around differences in patients who were performance status >2 difficult. Performance status did not yield any statistically significant results in the multivariable analysis ($p>0.1$), however it was left in the analysis as it was

felt that it could have been a confounder. Performance status had likely relationships with other variables, for example, it may have influenced treatment intent or the treatment given.

The findings of this study contradicted the large study by Sargent *et al.*, which suggested that higher performance status patients experienced higher levels of toxicity (Sargent *et al*., 2009). Despite being a large meta-analysis, Sargent *et al.* only looked at metastatic colorectal cancer and only found specific toxicities that this applied to. The population in this study was much more heterogeneous in terms of disease compared to Sargent *et al.*'s review, but also in terms of treatment intent and treatment used. Sargent *et al.* found that higher performance status patients had a higher all-cause mortality. This could also have been true for the population in this study, but such outcomes were beyond the reach of this research. The data used in Sargent *et al.*'s study would also include toxicity over a much greater period than the acute toxicity included in this research, so it was possible that if the population in this study were followed up over a longer period of time, the findings may have changed.

Performance status is a crude measure of functionality, yet remains a widely used clinical tool. A large number of factors could affect performance status, which extend far beyond any disability that may have occurred from cancer or chemotherapy. It is also possible that a patient could have several co-morbidities and still remain a low performance status and this highlights the limitations of such a measure. The literature may have led to the hypothesis that toxicity would increase with performance status, but the opposite was found. One theory to explain this was that patients of a lower performance status had fewer symptoms from their cancer or other diseases and so when a toxicity occurred, it was more noticeable and was thus reported. Many of the toxicities explored were very subjective and so inter-patient variability could have played a large role in explaining the differences in reporting of toxicity. Although it did appear that performance status influenced the occurrence of toxicity, further research would be required to elucidate the exact effects and to explore and control for, the other factors affecting performance status.

5.3.1.3 Toxicity and Disease

Different diseases affect patients in different ways and are associated with different symptoms (Neal and Hoskin, 2009). It was therefore theorised that the disease being treated could have an effect on toxicity.

Different diseases were associated with different rates of toxicity and initial descriptive statistics suggested that the differences between the groups was statistically significant ($p<0.05$). CUP, skin and sarcoma cancer patients were excluded from analysis due to the small numbers of patients, as it was felt that no meaningful conclusions could be drawn regarding this group of patients. Upper GI cancer patients had the highest rate of toxicity reporting, followed by breast cancer patients. Klute *et al.* found that malnutrition was predictive of toxicity in upper GI cancers, but no literature was found that reported an overall rate of toxicity (Klute *et al*., 2015). Similarly in breast cancer, no literature could be found that showed a study reporting the overall rate of toxicity, however Friese *et al.* did show that when surveyed, 872 (45%) of American women treated with chemotherapy for breast cancer reported a severe toxicity (Friese *et al*., 2017). This was severe according to the patient, so was of course a subjective measure, however an overall toxicity rate of 42.9% (186 patients) in breast cancer patients in this study was fairly similar, although many of those would have been grade 1 and not classified as severe by CTCAE criteria (National Cancer Institute, 2010).

A multivariable logistic regression analysis suggested that breast and upper GI cancer patients were significantly more likely to experience a toxicity than urology cancer patients ($p<0.05$), with a Pseudo-R^2=0.03, suggesting that the analysis explained a small amount of the variance in toxicity. No similar literature was found that compared toxicity rates amongst different diseases. Disease also appeared to have a significant effect on toxicity when included in multivariable regression analysis.

The disease being treated will dictate the regimen used and the treatment intent and so these variables must be considered when thinking about the effect of disease on toxicity. For example, adjuvant chemotherapy was not used in prostate cancer at the time of writing, but adjuvant chemotherapy accounted for 192 (43.8%) of the chemotherapy used in breast cancer. Different drugs were used in different diseases and as explored later in this study, the treatment used could have a significant effect on toxicity. Further research could include larger sample sizes for each disease and control for treatment and treatment intent.

5.3.1.4 Toxicity and Treatment Intent

Treatment intent can affect the regimen used to treat a cancer and the dose used. As such it was logical that it would affect toxicity. The three treatment intents had quite different numbers of patients, with over half of patients receiving treatment of palliative intent. Logistic regression analysis revealed an analysis with a very small pseudo-R^2 value of 0.003. This suggested that only a very small amount of the variance in toxicity could be explained by treatment intent alone. Neoadjuvant and adjuvant chemotherapy had higher rates of toxicity than palliative, and the regression analysis suggested that adjuvant chemotherapy carried a 21% higher risk of toxicity and neoadjuvant a 29% higher chance of toxicity than palliative chemotherapy. These predictions were not statistically significant, but could be considered of borderline significance as $p<0.1$ for each. Due to the differing sizes of the groups, it was possible that a larger sample size may have been required in order to produce statistically significant predictions. No literature was found that explored the effect of treatment intent on chemotherapy toxicity.

5.3.1.5 Toxicity and Treatment

Grouping treatments according to cytotoxicity yielded very unevenly sized groups, with 1416 (92%) of patients receiving a cytotoxic treatment. This made analysis difficult as a size effect could not be ruled out. Although the highest rate of toxicity was seen in patients who received a mixed treatment containing a cytotoxic and non-cytotoxic, this was not statistically significant ($p>0.1$). Other methods of grouping the treatments may have impacted on the number in the cytotoxicity groups. For example, all of the patients in the mixed group would have received a regimen with two or more drugs. It may have been possible with a larger sample to elucidate some predictions of statistical significance, however given the overlap of cytotoxicity with other groupings of treatments, this may not have been necessary.

The rate of toxicity increased as the number of drugs used increased and just under half of the patients who received 3 drugs experienced a toxicity. Spearman's correlation coefficient was 0.163 ($p<0.01$), suggesting a fairly strong correlation. The logistical regression analysis confirmed the relationship between the number of drugs and toxicity, with patients on 2 drugs being 50% less likely to experience a toxicity than those on 3 drugs ($p<0.01$) and those on one drug being 59% ($p<0.01$) less likely to experience a toxicity than those on a single agent. Little data was found on the number of drugs and the occurrence of toxicity, however Hurria *et al.* suggested that the number of drugs was a significant predictor of toxicity in older adults receiving chemotherapy (Hurria *et al*., 2011). Hurria *et al.*'s study included a variety of cancer diagnoses and treatment intents, but was confined to patients over 65 years of age. Each individual drug will be associated with a number of individual toxicities as reported in the summary of product characteristics and clinical trials. The addition of another drug will also result in a new group of adverse effects and as such there may be an increased risk of toxicity. It was possible that certain drugs may have potentiated the effects of others through pharmacodynamic and pharmacokinetic interactions, but these were not explored in detail in this study.

As mentioned above, the commissioning status of a treatment was felt to be of clinical significance. The main issue with this grouping was the inequality in size of the groups, with 1431 (93%) of patients falling in to the baseline-commissioning group. This meant that there was a large size effect and as such conclusions could not be drawn around the effect of commissioning on toxicity. A much larger sample size would be required to explore if commissioning status does have a relationship with toxicity, although clinically this is unlikely.

Emetogenicity is highly clinically significant. It was expected that the higher the emetogenicity of a regimen, the more toxicities would be seen, as more patients would be reporting nausea or vomiting. The data confirmed this suspicion. The highly emetogenic group had a higher rate of toxicity than the other groups and the higher the emetogenic potential, the higher the rate of toxicity. This was confirmed by logistic regression analysis, which suggested that moderate emetogenic drugs had a 29% ($p=0.01$) lower chance of toxicity than those on highly emetogenic treatments. The risk reduced further to 42% ($p<0.01$) for low emetogenic and 64% ($p=0.02$) for minimally emetogenic treatments. These predictions were statistically significant. It should be noted that the minimally emetogenic group only had 7 patients who reported a toxicity and so the group was significantly smaller than the others. A larger sample size would be required to confirm the findings for the minimally emetogenic group as when combined with other variables in the multivariable regression analysis, emetogenicity did not have a significant effect on toxicity ($p>0.1$).

5.3.1.6 Multivariable Logistic Regression for toxicity

This was performed using the predictors that had been shown independently to have an effect on toxicity. The sample was controlled for age and confirmed that a number of predictors had a statistically significant relationship with toxicity. The pseudo $R^2 = 0.04$, which, although still small, was higher than those of the individual values. Once other variables were included, performance status did not yield any statistically significant predictions ($p>0.1$).

Treatment intent was not included in the analysis as the univariate analysis explained such a small amount of the variance. It was, however, suspected that it could have an effect, but would interact with other variables. Only certain regimens were given within each intent, so it is likely that if a treatment was having an effect on toxicity, then treatment intent would be considered within that treatment type. Disease may have also played a role in the treatment intent. Adjuvant or neoadjuvant chemotherapy is only used in certain diseases and as such the variables of treatment intent and disease interact. Treatment intent could also be related to performance status. Patients with a higher performance status may have been less likely to receive chemotherapy of curative intent as they may have been deemed unable to tolerate a rigorous treatment of curative intent.

Cytotoxicity of treatment and commissioning status were not included in the multivariable analysis as they had not been shown to have a relationship independently with toxicity. Also, as described above, these variables had a degree of overlap with other methods of grouping treatments.

The multivariable analysis confirmed that as the number of drugs increased, so did toxicity. Those patients who received a single agent treatment were 54% less likely to report a toxicity than those on 3 drugs ($p<0.01$) and those on 2 drugs 35% less likely ($p=0.05$). Disease played a significant role in predicting toxicity with an overall $p=0.01$. Breast and upper GI cancer patients had higher

toxicity rates than urological and other diseases, which were statistically significant ($p<0.05$). Many factors could have been at play here. The disease would dictate the treatment used and possibly the intent of treatment. Some patients may have recently had surgery, especially in the adjuvant treatment intent and as such may have been predisposed to toxicity or already experiencing the symptoms covered by the toxicity assessments before chemotherapy was given. Disease itself could have been responsible for certain toxicity symptoms. For example, in upper GI malignancy, nausea or vomiting could be caused by disease rather than treatment. In order to further explore the true relationship of these symptoms with chemotherapy, further research would be needed to assess symptoms at baseline and then following chemotherapy, to allow for comparison.

5.3.2 Grade of Toxicity

The grade of toxicity according to CTCAE criteria (National Cancer Institute, 2010) is a measure of the severity of a toxicity. The majority of toxicities were grade 1 with grade 3 and 4 toxicities only accounting for 7 (1.3%) of toxicities reported. The numbers of patients reporting a grade 3 or 4 toxicity was too small for any meaningful analysis, but it should be remembered that this study only included acute toxicity within the first 24 hours following chemotherapy. It was possible that higher grade toxicities may have occurred later after chemotherapy, indeed this could have been true for all grades of toxicity. The hypothesis that more low grade toxicities would be seen than high grade was proved correct, with low grade accounting for 523 (99%) of toxicities reported. It was theorised that the severity of toxicity would follow the areas in which higher rates of toxicity were reported. Although true in some instances, this did not always follow for all predictors.

5.3.2.1 Grade of Toxicity and Age

Age was analysed in two ways. Firstly as a continuous variable where the mean was compared, but this treated age as an outcome rather than a predictor. The second method was to group age and treat it as a categorical variable. The data gave contradictory conclusions about the relationship of age and toxicity. It appeared that the mean age of patients experiencing each grade of toxicity was fairly similar, although there were subtle differences. Ordinal logistic regression analysis of age as a continuous variable did produce a statistically significant odds ratio, suggesting that for every year of age increase, there was a 2% decrease in the grade of toxicity ($p=0.04$). This was a small effect but over large differences in age was likely to have an effect clinically.

When categorising age into groups, it was difficult to pick up any pattern from the data. For grade 1 toxicities, the rate appeared to increase with age up to the 71-80 year old group. The same was not true for grade 2 toxicity, which did not seem to follow a pattern in terms of differences between the age groups. Ordinal logistic regression analysis did not produce any statistically significant predictions of grade of toxicity ($p>0.1$).

In a review of 242 prescriptions for chemotherapy in phase I clinical trials, LoConte *et al.* found that age was not predictive of the severity of toxicity (LoConte *et al*., 2009). The results of this study would agree, however true comparison could not be made as LoConte *et al.* only looked at phase I trials, which would have introduced a selection bias into the population as all patients would have had to fulfil the trial entry criteria, which was likely to require a good performance status and exclude many co-morbidities, disease states and other variables.

It was possible that age did affect the grade of toxicity, but this study did not produce robust enough data to conclude that age had an effect on the severity

of toxicity. Indeed, the data did not reveal that age influenced the occurrence of toxicity, but it was possible it affected severity. There was little available literature to suggest that age affected the severity of toxicity and the literature was contradictory as to the effect of age on the occurrence of toxicity.

5.3.2.2 Grade of Toxicity and Performance Status

This study has seen that performance status alone seemed to affect the occurrence of toxicity but when other variables were taken into account, no statistically significant predictions were seen ($p>0.1$). The data suggested that for grade 1 toxicities, the higher the performance status, the less grade 1 toxicities were seen. This was not true for grade 2 toxicities and regression analysis could not produce any statistically meaningful predictions. It was possible that performance status influenced grade of toxicity, but a larger sample size would be required to prove this, as more performance status >1 patients would be needed in order to prove any relationship. Again, the small number of grade 3 and 4 toxicities made it impossible to draw any conclusions.

The only study found in the literature regarding performance status and grade of toxicity was Sargent *et al.*, who studied patients with metastatic colorectal cancer and found higher rates of grade ≥3 nausea and vomiting in patients who were performance status 2 or above (Sargent *et al*., 2009). It was very difficult to find comparisons with this study as it only included colorectal cancer patients who underwent chemotherapy of palliative intent. Another study found that malnutrition was predictive of patients with a GI malignancy receiving lower doses of chemotherapy due to toxicity, but the grades of toxicity were not explored and so it was difficult to extrapolate the findings regarding co-morbidity to this research (Klute *et al*., 2015).

From the literature and the findings from the data in this study, it was not possible to associate performance status with grade of toxicity.

5.3.2.3 Grade of Toxicity and Disease

Disease was found to be predictive of the occurrence of toxicity, so the potential relationship between disease and grade of toxicity was explored. The different diseases showed significantly different rates of each grade of toxicity, however univariate ordinal logistic regression analysis failed to show any statistically significant predictions ($p>0.1$). When entered into a multivariable ordinal logistic regression analysis, the disease was shown to be a predictor of grade of toxicity. This would suggest that other variables needed to be controlled, in order to illicit the effect of disease on grade of toxicity. Urology, gynaecology and lung cancer patients were all shown to report a higher grade of toxicity than breast cancer patients. It was decided to use breast as the reference group, as this was the largest group and a group in which a good number of toxicities was reported and so was felt to be an appropriate comparator. As described above, disease was linked to a number of other factors including performance status, age, treatment used and treatment intent. It was clear from the data that lung cancer patients tended to have a higher performance status than other tumour sites, which may have contributed to the severity of toxicity, however the same was not true for urology or gynaecology cancer patients. It was possible that the treatments used in the diseases may have played a major role in the severity of toxicity experienced. No specific data in the literature, concerning the link between disease and toxicity was found, as many studies focused on one particular disease or treatment. Disease was a particularly wide variable and within each disease there was a wide variety of patients with different problems, symptoms and co-morbidities. For example in breast cancer there may have been some relatively healthy patients undergoing adjuvant chemotherapy, with no co-morbidities or patients with very advanced cancer who had a number of symptoms from their cancer and a poorer performance status. All of these factors may have influenced toxicity and its severity. It was also impossible from this data to distinguish symptoms arising due to chemotherapy toxicity or from other causes such as disease or co-morbidities. Only a toxicity assessment at baseline would have helped to differentiate this.

5.3.2.4 Grade of Toxicity and Treatment Intent

The research revealed no significant link between toxicity and treatment intent and did not reveal any statistically significant relationship between the severity of toxicity and treatment intent ($p>0.1$). No obvious differences were seen in the rates of each grade of toxicity. It could be theorised that adjuvant and neoadjuvant treatments were more likely to produce a higher grade of toxicity, as higher doses of more intensive treatments tended to be used. There was a large body of evidence suggesting that toxicity is closely related to dose (Frei and Canellos, 1980) and so it would follow that the higher the dose, the more likely and more severe toxicity was. Adjuvant and neoadjuvant chemotherapy patients were also more likely to be fitter as seen with the distribution of performance status, which could affect the severity of toxicity. As cure or prevention of recurrence is the aim of neoadjuvant or adjuvant chemotherapy, more toxicity may be tolerated than in palliative treatment where quality of life is a more significant goal (Neal and Hoskin 2009). However this was not evident from the data. It was possible that higher grade toxicities may have occurred later than the 24 hour period which was included in this research. Further research would need to follow patients up over a longer period of time. It was also possible that higher grade toxicities may have occurred in subsequent cycles, rather than the first, which were not captured by the data in this study.

5.3.2.5 Grade of Toxicity and Treatment

As with toxicity, the cytotoxicity of treatment did not reveal any significant differences in the grade of toxicity ($p>0.1$), probably because of the uneven spread across the groups. It was not possible to draw any conclusions regarding this and no literature was found that explored the cytotoxicity of treatment and toxicity.

The number of drugs had a significant impact on the occurrence of toxicity, but ordinal logistic regression was not able to show any statistically significant relationship between the number of drugs and the grade of toxicity ($p>0.1$). A Spearman's correlation coefficient of 0.168 ($p<0.01$) was found, which did

suggest that as the number of drugs increased, so did the grade of toxicity, however this was the only statistically significant relationship found. This was probably due to the low numbers of grade 3 and 4 toxicities and as such a larger sample size would be required to further explore the relationship and prove that there was no type 1 error. It may be that if a longer follow up time of toxicity was undertaken, then more grade 3 and 4 toxicities would occur and analysis would be more feasible. The higher likelihood of toxicity with the more drugs used was clear, so it would follow that the more drugs used, the more severe a toxicity is likely to be. If two drugs cause the same toxicity then it may be that an additive effect is seen, however evidence for this is beyond the reach of this research.

As with the occurrence of toxicity, it was not possible to find any link between commissioning status of chemotherapy and severity of toxicity and this was also something for which no literature was found.

There was a strong relationship between toxicity and emetogenicity, as predicted. It was expected that this would also have a significant effect on the severity of toxicity, however the data was unable to prove such a relationship ($p>0.1$). The method for classifying regimens according to emetogenicity is based on risk and the international guidelines used are designed to prevent the degree of vomiting, which would suggest that emetogenic potential is related to the severity of nausea and vomiting (Basch *et al*., 2011). The small numbers of grade 3 and 4 toxicities reported, made it difficult to identify any differences between the emetogenic groups. A larger sample size or a longer follow up would be required to elucidate this. This research only considered acute emesis, within 24 hours of chemotherapy and delayed emesis is a well-documented sequala of chemotherapy (Hesketh, 2008), meaning that there would have been a number of instances of toxicity which were not recorded in this data. The effect of other toxicities on the data should also be considered. Non-nausea or vomiting toxicities were included in the data, which would have been unlikely to have been affected by the emetogenicity of a chemotherapy regimen, which will have had a significant effect on the data. Nausea and

vomiting accounted for 230 (43.4%) of the toxicities reported, meaning that the majority of toxicities would be unrelated to the emetogenicity of chemotherapy. However it was possible that if nausea or vomiting was present, it could lead to other toxicities such as pain or fatigue, but no data was seen to support this theory. The specific data regarding nausea and vomiting was explored later on.

5.3.2.6 Multivariable Ordinal Logistic Regression of Grade of Toxicity

As grade of toxicity was an ordinal variable, ordinal logistic regression was employed. Other than for age, no statistically significant predictions were seen in the independent regression analyses ($p>0.1$). When all factors were considered together, the analysis did suggest some statistically significant relationships ($p<0.05$). The pseudo-R^2=0.02, suggested that the analysis still left a large amount of variance in the data unaccounted for. The disease seemed to have an effect on the grade of toxicity as discussed above. This was as expected and could have been due to a variety of reasons. The literature has suggested that higher performance status is associated with more toxicity of severe grades in some cancers, but this research was unable to corroborate this (Phaibulvatanapong *et al*., 2018). Disease also appeared to have an effect on the severity of toxicity. Breast cancer patients was the biggest group, meaning that there may have been a size-effect, however breast cancer patients had a higher percentage of patients who were performance status 0 than any other group. Breast cancer patients also received more adjuvant or neoadjuvant chemotherapy than any other group, which could have had an effect on grade of toxicity, although this research was unable to prove this. FEC was the most frequently used regimen in the population and this was exclusively a breast regimen. FEC is highly emetogenic and so this could have had an effect on the grade of toxicity reported if nausea or vomiting were experienced, but again, it was not possible to prove this statistically using this research.

5.3.3 Hospital Admission within 30 days of Chemotherapy

As described earlier, hospital admission is a possible consequence of chemotherapy toxicity, which can have implications for the patient but also the wider healthcare system. Hospital admissions were identified through the patient management system at NUH and only admission due to toxicity type symptoms were included. As with toxicity, it was not possible to differentiate between admissions due to symptoms of toxicity and those due to symptoms similar to toxicity but due to another cause such as disease.

There was a significant number of hospital admissions, with 203 (13.1%) of patients being admitted. This accounted for a significant proportion of inpatient capacity within the oncology department at NUH and as such was a necessary area to research given the financial and operational implications. The effect of hospital admission on patients was not readily described in the literature in terms of comparisons of outcomes with patients not admitted. The reasons for hospital admission were fairly varied with 37 different reasons. Some of these reasons had overlap and so were consolidated for presentation in **Table 32**. Many of the reasons for admission only applied to a single patient, making comparison very difficult.

For the purposes of analysis, hospital admission was treated as a binary variable. This showed the patients who were admitted within 30 days of the first cycle of chemotherapy. Thirty days may have been an arbitrary number, but was based on the 2008 report of mortality within 30 days of chemotherapy (Mort *et al*., 2008). It was also a measure used in clinical practice, both nationally and locally. At NUH all patients who die or have a critical care admission within 30 days of a cycle of chemotherapy, have their case discussed at a monthly morbidity and mortality meeting and the measure is felt to be highly relevant to clinical practice. The mean number of days that patients were admitted following the first cycle of chemotherapy was 8.2 (SD= 5.6), which suggested that the admissions seen may not have been due to the toxicities reported in this dataset as they only covered the first 24 hours after

chemotherapy. Only 9 patients were admitted within the first 24 hours of chemotherapy. It could have been the case in some instances that admissions were due to the acute toxicities reported, that worsened in the period after chemotherapy, necessitating admission.

Very little literature was found regarding hospital admission due to chemotherapy toxicity and so making comparisons to this data was not possible in many instances.

5.3.3.1 Hospital Admission and Age

As with toxicity, age was analysed as a continuous variable and also as a categorical variable. There was no difference in the mean age of those patients who were admitted, compared to those who were not. The rate of admission was highest in the 51-60 year old age group and lowest in the 41-50 year old age group, but a logistical regression analysis was not able to prove a statistically significant relationship between age and admission ($p>0.1$). Benard-Laribiere *et al.* found that patients admitted with an adverse drug reaction were significantly older than those admitted for other reasons (Bénard-Laribière *et al*., 2015), however this study was over a small period of time and was not specific to chemotherapy, so true comparison was not possible. A larger sample size would be required in order to further explore the effect of age on hospital admission within 30 days of chemotherapy. Not all toxicity requires admission. It may have been that higher grades of certain toxicities could be managed at home, whereas lower grades of other toxicities necessitated hospital treatment.

5.3.3.2 Hospital Admission and Performance Status

No statistically significant differences were seen in admission rates between the performance status groups ($p>0.1$). The higher performance status groups had small numbers of patients and so a larger sample size would be required to establish any effects of performance status on admission. Aliyu *et al.* suggested that in a general population that included people without a cancer diagnosis, people with an impairment of functional state had a higher risk of hospital admission (Aliyu *et al.*, 2003). It could not be taken from this that patients with a poorer performance status had a higher risk of admission due to chemotherapy toxicity, as there were many other variables not included in the research that would apply to patients on chemotherapy. Aliyu *et al.* also only looked at elderly patients, so the population was not comparable to the population in this research. It was therefore not possible to make any judgement on the effect of performance status on hospital admission.

5.3.3.3 Hospital Admission and Disease

Admission rates were different amongst the different disease groups with upper GI and lung cancer patients having the highest rates of admission. As with toxicity, CUP, skin and sarcoma were omitted from analysis due to the very low numbers. Pearson's X^2 test showed that the differences between the groups were statistically significant ($p<0.01$). The lowest rate of admission was seen in the urology cancer patients. A univariate logistic regression analysis produced significant predictions, confirming that gynaecology ($p=0.02$), head and neck ($p<0.01$), upper GI ($p<0.01$) and lung cancer patients ($p<0.01$) were all more likely to be admitted than the reference group, which was urology cancer patients. Pseudo-$R^2 = 0.02$, suggesting that the analysis only explained a small amount of the variance in admission rates. These effects continued to be seen in a multivariable regression analysis, suggesting that disease was a predictor of hospital admission. As stated previously, it was not possible to distinguish between admission for true chemotherapy toxicity and admission due to symptoms from another cause such as disease. There was also the possibility that patients had undergone another modality of treatment such as surgery or radiotherapy that could account for the symptoms. The four diseases that were

associated with a higher risk of admission, are associated with a wide variety of symptoms which could overlap with the symptoms of toxicity (Neal and Hoskin, 2009). As with the other outcomes, disease will dictate a number of other variables such as treatment intent and the treatment used. In order to explore the relationship between disease and hospital admission further, it would be necessary to measure baseline toxicities then measure again after chemotherapy to identify those symptoms arising from toxicity.

5.3.3.4 Hospital Admission and Intent of Chemotherapy

There did not appear to be significant differences in the admission rate between the different intents of treatment and a logistic regression analysis confirmed this ($p>0.1$). This was not unexpected as it was not possible to prove a link between treatment intent and toxicity or severity of toxicity. With a larger sample size, wider variances may have been seen and as described previously there was a likely interaction of treatment intent with other variables.

5.3.3.5 Hospital Admission and Treatment

The effect of treatment on admission was explored. As it was expected that toxicity would differ between different treatments, it was also anticipated that this would be true for admission.

Again the wide variance in the sizes of the groups when treatment was grouped according to cytotoxicity, meant that comparing the groups was difficult, with only one admission in the non-cytotoxic group. However, logistic regression analysis gave a pseudo-$R^2 = 0.06$, suggesting that the analysis did go some way to explaining some of the variation between admission rates but left a large amount of the variance unexplained. Patients on non-cytotoxic chemotherapy appeared 10% less likely to be admitted than those on a mixed regimen. Although this difference was statistically significant ($p=0.02$), it was difficult to ascertain how this would be useful to clinical practice as the groups were very broad.

As toxicity increased with the number of drugs used, it was anticipated that admission rates would be higher with the more drugs used. This was shown not to be the case, with patients who received two drugs having the highest admission rate. Logistic regression analysis showed that those on 2 drugs were 63% more likely to be admitted than those on 3 drugs ($p<0.01$), which did not follow the same pattern as toxicity. It may have been that delayed toxicities were higher in these patients, but this was not recorded in this research. It was also possible that the patients admitted in the 2 drug group were admitted for symptoms not due to toxicity, but without a baseline toxicity assessment, it was not possible to establish this. Another possibility was that the 2 drug regimens contained more toxic agents or agents associated with symptoms requiring hospital admission.

As with toxicity, no statistically significant relationship was seen with hospital admission and commissioning status of chemotherapy ($p>0.1$). As the cancer drugs fund is costly and the benefits of its use have been under question (Aggarwal *et al*., 2017), establishing the additional costs and burden of resources associated with it, such as admission due to toxicity, was important. Unfortunately this research was not able to establish any conclusions regarding this.

As emetogenicity was associated with toxicity, it was expected that it would have an effect on hospital admission. However, nausea and vomiting was the reason for admission in 20 cases with diarrhoea and vomiting being cited as the reason for another 5 admissions. It was therefore not unexpected that a statistically significant relationship could not be identified between emetogenicity and hospital admission ($p>0.1$). Patients on moderately emetogenic drugs had a higher rate of admission than the other groups, but logistic regression did not reveal any statistically significant predictions ($p>0.1$).

5.3.3.6 Multivariable Logistic Regression of Hospital Admission

The factors that had shown relationships with hospital admission were included in a logistic regression analysis controlled for age. The analysis had pseudo-R^2 = 0.02, suggesting that a small amount of variance was explained by the analysis. The number of drugs had an overall significant p-value (p=0.04), with patients on 2 drugs being more likely to be admitted to hospital than those on 3 drugs. This was contradictory to the findings for toxicity, where the more drugs used, the more toxicity was seen. It could be that with a larger sample size, the effect of number of drugs on hospital admission would become clearer.

Disease was the only other factor that had a significant impact on hospital admission. As in the individual analyses, patients with gynaecological (p=0.02), head and neck (p<0.01), upper GI (p<0.01) and lung cancers (p<0.03) had significantly higher rates of admission than the reference group, which was urology. The size of the effects were also large, suggesting that disease had a significant impact on the risk of admission. As explained earlier, it was not possible to distinguish between admissions truly due to chemotherapy toxicity and those due to symptoms from other causes. The analysis controlled for age and treatment by the number of drugs, but it did not include any other variables, which may have had an effect on admission. Other variables could have an effect within disease such as intent of treatment and treatment used (if grouped in alternative ways). A larger sample size or investigating admission over a prolonged period may yield more robust data that could confirm the true effect of the other variables on admission. The disease sites that had higher admission rates, were those sites associated with higher grades of toxicity, which agreed with the initial hypothesis.

5.3.3.7 Toxicity and Hospital Admission

In order to assess the effect of the toxicities reported on hospital admission, the patients experiencing a toxicity were separated from the rest of the population. Of those patients who reported a toxicity, 77 (14.2%) were admitted. This was in comparison to a rate of 13.1% (203 patients) for the entire population and

12.8% (125 patients) for those patients who did not experience a toxicity. A logistic regression analysis did not yield any statistically significant prediction around admission and toxicity ($p>0.1$). It may have been that delayed toxicity played more of a role in predicting the risk of admission, but this was not included in this research.

The grade of toxicity seemed to have an effect on hospital admission with higher rates of admission seen in the higher grades of toxicity, however the size of the groups did not allow for any reliable assumptions to be made. It may have followed that the more severe a toxicity, the more likely a hospital admission was, as it could require more intensive intervention. By definition, a grade 3 toxicity is severe or medically significant and indicates hospitalisation or prolongation of hospitalisation and grade 4 toxicity is life threatening (National Cancer Institute, 2010).

It was seen that upper GI cancer increased the risk of experiencing a toxicity, the upper GI group also had higher risk of admission in regression analysis. This was not true for other diseases. Gynaecology and lung cancer patients were more likely to report a higher grade of toxicity according to the ordinal regression analysis in **Table 31**. These disease groups were also shown to have a higher rate of admission in the analysis in **Table 35**. It may have been that the original hypothesis of higher rates of hospital admission being seen where higher grades of toxicity were seen was correct, however beyond the parameter of disease, this research was not able to demonstrate any further relationships. A larger sample size with more patients experiencing grade 3 or 4 toxicity would allow further elucidation of this.

5.3.4 Length of Stay

The length of stay was investigated for all patients who were admitted. In order to do this, patients who were admitted were separated from the rest of the population. The median length of stay was 3 days for the entire population. No

data was found in the literature, which reported a length of stay following admission for a chemotherapy related toxicity in a general population. Cuppens *et al.* reported a mean length of stay of 9.5 days for lung cancer patients admitted to hospital, but this was only a single disease and included admission for disease related effects as well as toxicity so could not be compared (Cuppens *et al*., 2016). It was seen that some of the factors explored had an effect on the risk of hospital admission, so it was suspected that length of stay would also be affected. Due to time constraints, and given that there were not a large number of hospital admissions, only descriptive statistics were employed in order to explore length of stay. Regression analysis did not prove possible for this research, but may be an area for future research to focus on. Length of stay has clear implications for both patients and the health economy and so is an important area for research to focus on.

Many factors may affect length of stay as described by Clarke (Clarke, 1996). There are obvious implications on the health economy and the patient. Patient factors such as co-morbidity and disease severity affect length of stay, as do healthcare system factors such as geographical location, physician practice style and method of payment. When considering length of stay in a wider context than the NHS, it is important to consider these factors.

5.3.4.1 Length of Stay and Age

As previously, age was analysed as a continuous variable and also as a categorical variable. Median length of stay was highest in the 21-40 year old age group and lowest in the over 70 year olds, but both of these groups had far fewer admissions than the other groups, so this may have affected the data validity. For the rest of the groups, the median length of stay was fairly similar and was close to the median for the population. Kruskall-Wallis test gave $p=0.29$, confirming that the differences between the groups was not statistically significant.

When treating age as a continuous variable, a statistically significant Spearman's correlation coefficient of -0.146 was seen (p=0.04), suggesting that as age increased, length of stay decreased slightly. This was unexpected as it was known that older patients were more likely to have co-morbidities and be potentially more frail and less able to tolerate chemotherapy (Hurria, 2014). The literature was contradictory around age and toxicity, although several sources suggested that older patients were more vulnerable to toxicity. It could therefore have been theorised that admission could have been more likely and length of stay longer in older patients as they were less able to tolerate toxicity than younger patients. However the data in this research was not able to draw conclusions around the relationship of age and length of hospital stay.

5.3.4.2 Length of Stay and Performance Status

Performance status did not appear to affect length of stay with no statistically significant differences seen between the groups (p>0.1). The low numbers of patients in the performance status >1 groups meant that there was not enough data to reliably identify any relationships. Co-morbidity was suggested as a factor that affects length of stay by Clarke (Clarke, 1996), but this research was unable to reach any conclusions regarding this.

5.3.4.3 Length of Stay and Treatment Intent

It was not possible to show a link between toxicity, severity of toxicity or admission and treatment intent. The distribution of patients in each group was varied and as such made comparison difficult. The median length of stay did appear significantly shorter in the neoadjuvant group and this group had a much smaller standard deviation than the other groups, so it may have been that patients receiving neoadjuvant chemotherapy had a shorter length of stay than other patients. This was of borderline statistical significance (p=0.09). As discussed previously, intent of treatment was linked to a number of other variables. The neoadjuvant group had the highest proportion of performance status 0 patients, suggesting that patients in this group were generally fitter than patients who received palliative or adjuvant chemotherapy. Neoadjuvant

chemotherapy was used in only a few of the diseases and so disease may have had an effect within these groups. A larger sample size obtained by looking at admissions in another centre or over a longer period of time would be required to confirm this suspicion.

5.3.4.4 Length of Stay and Disease

The length of stay was quite different among the different disease groups, but these differences were not statistically significant ($p>0.1$). Again the numbers in each group was low and the variance in each group fairly wide. There was little available literature for comparisons, although interestingly, median length of stay in the lung cancer patients was 2 days, which was significantly lower than the 9.5 days reported by Cuppens *et al.*, however that study included admissions for reasons other than chemotherapy toxicity, so direct comparisons could not be made (Cuppens *et al*., 2016). Clarke suggested that severity of disease was a factor that affected length of stay, however this was not recorded in the data in this research and so could not be commented upon (Clarke, 1996). Clarke's review was also of a much more general population and not restricted to chemotherapy toxicity as this research was. Further data, possibly from additional centres would be needed to further assess the effect of disease on length of stay. Data from other centres would allow a control for variance in local practice to be introduced and a national database would allow for trends be monitored across multiple localities.

5.3.4.5 Length of Stay and Treatment

When grouped according to cytotoxicity, drug class and commissioning status, there were no statistically significant variations in length of stay ($p>0.1$).

When grouped according to number of drugs, length of stay was significantly shorter, the higher the number of drugs used. There were a larger number of patients in the group who received 2 drugs, but the other two groups had similar numbers of patients. Spearman's correlation coefficient gave a

statistically significant correlation coefficient of -0.149 (p=0.04), which suggested that there was an inverse correlation between the number of drugs and length of stay. This was an unexpected finding, as toxicity and severity of toxicity both increased with the number of drugs used it was anticipated that admission rate and length of stay would also increase, however the opposite was true. It may have been that the toxicities seen in the patients receiving higher numbers of drugs were self-limiting or managed at home, rather than necessitating admission. It could also have been that the toxicities that did result in hospital admission, were more easily and quickly managed in the patients receiving a higher number of drugs than those who received fewer drugs. The groups in the number of drugs all had wide variances but had similar standard deviations, so it was likely that they were comparable.

When grouped according to emetogenicity, length of stay was significantly different between the groups (p=0.03). Length of stay appeared to reduce the higher the emetogenicity of a regimen. The minimally emetogenic group could not be considered in the analysis as it contained only one patient. Each group had a wide variance. All toxicities were included in this analysis and as pointed out previously, admissions for reasons other than nausea or vomiting were included, which may have skewed the data. Also the toxicity reported in this study would only include acute nausea or vomiting and so it was probable that many of these admissions were for delayed nausea or vomiting. No data was available in the literature for comparison of admission or length of stay in chemotherapy induced nausea and vomiting.

5.4 Sub-group Analyses

Following on from the primary outcome measures, sub-group analyses were undertaken to further explore the data according to the three largest tumour groups and the three most frequently reported toxicities.

5.4.1 Breast Cancer

Breast cancer patients were the largest group of the study population and national data suggested that high levels of chemotherapy are used in breast cancer patients (Chemotherapy Intelligence Unit, 2014). Breast cancer is also known to be the most common cancer in females in the UK (Cancer Research UK, 2014). This means that toxicity could have wide implications for the healthcare provider and the health economy.

The age distribution was not too dissimilar from the whole population with a peak incidence between 51 and 70 years old. This was as expected, as the UK has a national breast screening programme between the ages of 50 and 70 for all women (England, 2018) and these age groups see the highest number of cases, despite incidence of breast cancer increasing with age (Cancer Research UK, 2015c). The mean age of the breast cancer patients was 59.1 years (SD= 11.5), which was slightly younger than the mean for the entire population of 63.2 (SD=11.4) years. Nearly three-quarters of patients were performance status 0, which was higher than the 50% for the whole population, suggesting that breast cancer patients were perhaps fitter then the rest of the population. This could have been explained by the fact that the majority of patients in the breast group received adjuvant or neoadjuvant chemotherapy. This would mean that they had localised disease, which was unlikely to impair function, as perhaps a localised lung cancer might. It was probable that this group of patients had fewer co-morbidities than other disease groups, such as in lung cancer where smoking is prominent (Cancer Research UK 2015f).

Breast cancer patients received a wide variety of different regimens, which introduced a variable that may have had a significant effect on the outcomes for breast cancer patients, but which also created a large number of groups, making comparison difficult. Treatments were grouped according to the methods that the whole population was subjected to. Over 60% (278 patients) of breast cancer patients received a regimen containing 3 drugs. This was as expected as it was seen that FEC was the most common regimen used and this was solely used in breast cancer. This was a contrast to the whole study population where the majority of patients received a 2-drug regimen. The breast cancer patients received a significantly higher percentage of highly emetogenic chemotherapy than the whole population and this was largely due to the high usage of FEC, which as an anthracycline/cyclophosphamide combination, is classed as highly emetogenic (Basch *et al*., 2011).

5.4.1.1 Toxicity in Breast Cancer

Toxicity of any grade was reported by 180 (42%) of breast cancer patients, which was slightly higher than 530 (35.6%) for the general population. As with the whole population, the breast cancer patients reported nausea, vomiting and fatigue most frequently. There was little comparable literature found that evaluated the overall incidence of toxicity. Friese *et al.* stated that when 1945 American patients with breast cancer treated with chemotherapy were surveyed, 875 (45%) reported a toxicity that they considered severe (Friese *et al*., 2017). This included delayed toxicity and toxicity beyond the first cycle of chemotherapy, neither of which this study recorded. Friese *et al.* used a questionnaire completed by patients, which could also have had an effect on the results when compared to this study, where nurses completed a telephone assessment of toxicity. There may have been differences in rates of reporting depending on the method of reporting. No literature was found to support this theory. Schonerr *et al.* found that only 7 (0.9%) of patients had an absence of toxicity, however this included delayed toxicity, which was beyond the scope of this research (Schönherr *et al*., 2012).

Multivariable logistic regression was undertaken based on the factors shown to affect toxicity in the whole population. The analysis yielded pseudo-R^2=0.06, suggesting it explained some of the variance in toxicity, whilst leaving a large amount of variance unexplained. The only statistically significant prediction from the analysis was around the number of drugs given. Patients on one drug were significantly less likely to experience a toxicity than those on three drugs (p=0.02). This was the same as for the whole population. The most commonly used three -drug regimen used in breast cancer patients was FEC, which accounted for 58.7% (257 patients) of all chemotherapy given to breast cancer patients. This suggested a large size effect, meaning that true comparison may not have been possible. However FEC is known to be highly emetogenic and associated with a high incidence of toxicity, so it was not unexpected that FEC produced higher levels of toxicity (Hesketh *et al.,* 2017a). The vast majority of FEC treatments were of adjuvant or neoadjuvant intent, which may have affected the levels of toxicity reported. It is known that dose has a significant impact on the occurrence of toxicity (Frei and Canellos, 1980), but this was not recorded in the research. It may have been that different doses were used for different treatment intents. Booth *et al.* suggested that age younger than 40 years, nausea expectation, not eating before treatment and low alcohol use were risk factors for nausea and vomiting in 143 patients treated with chemotherapy for breast cancer (Booth *et al*., 2007). This was a small study and included delayed toxicity and factors not recorded in this research, so direct comparison of results was not possible.

No other factors were shown to have a statistically significant effect on toxicity in the breast cancer patients (p>0.1). In order to explore this further, a larger sample size would be required, or recording of toxicity for a longer period in order to obtain information on delayed toxicity.

5.4.1.2 Grade of Toxicity in Breast cancer patients

Reporting rates for each grade of toxicity were similar in the breast cancer patients to those for the whole population. No grade 3 or 4 toxicities were

reported. Some of the regimens used in breast cancer are known to be associated with high levels of nausea and vomiting and this can be in the form of acute emesis (Hesketh, 2008), so it was expected that some higher grade toxicities would have been seen, but this was not the case. It could be that higher grade toxicities were seen beyond the first 24 hours after chemotherapy when the nurse assessment of toxicity took place. This finding concurred with the study by Schonherr *et al.*, which reported low rates of grade 3 or 4 toxicities in patients on FEC chemotherapy, which made up the majority of the breast cancer patients in this study (Schönherr *et al*., 2012).

Ordinal logistic regression analysis was undertaken to explore the relationship between the predictors and the grade of toxicity seen in breast cancer patients. The same factors were included in the analysis that were used in the analysis when looking at toxicity severity in the whole population. As with toxicity, the only statistically significant prediction was with the number of drugs. It was seen in the previous analysis that the more drugs given, the higher the rate of toxicity reporting ($p<0.01$). It also appeared that the higher the number of drugs given, the more severe a toxicity was likely to be, although this was not statistically significant ($p>0.1$). This was as expected, and FEC account for nearly all of the 3 drug regimens in breast cancer patients (East Midlands Cancer Alliance 2018). The Friese *et al*. study reported that 872 (45%) of women receiving chemotherapy for breast cancer reported a toxicity as severe (Friese *et al*., 2017), but it was not possible to make a direct comparison to this research, as in the Friese *et al.* study, toxicity was not reported in terms of CTCAE criteria as it was in this study (National Cancer Institute, 2010), so what was severe in one study, may not have been classed as severe in another. No other data pertaining to the grade of toxicity in breast cancer patients was found.

5.4.1.3 Hospital Admission and Length of Stay in Breast cancer patients

Breast cancer patients had a slightly lower admission rate than the general population, and median length of stay was the same. No significant predictors

of admission were found (p>0.1). The only data found in the literature, pertaining to admission in breast cancer patients, was by Pittman *et al.* and was a small single-centre study that reported an admission rate of 13% (19 patients) (Pittman *et al*., 2015). This was slightly higher than the 10.3% reported in this study, but Pittman only included those patients treated with curative intent, whereas this study included those who received palliative chemotherapy, which was likely to impact the data for reasons discussed previously. None of the data suggested that admission rate or length of stay was particularly different in the breast cancer patient group compared to the whole population and no literature around general admission rate and length of stay was found for breast cancer patients. The studies reporting toxicity in breast cancer patients did not report any admission or length of stay data.

5.4.2 Colorectal

Colorectal cancer patients were the second biggest disease group, accounting for a fifth of the study population. Within this group there were several diagnoses including colorectal and anal cancer. The number of patients seen in this group compared with cancer incidence data with colorectal cancer being the third most common cancer in men and women in the UK (Cancer Research UK, 2014). According to national data, colorectal cancer was the second largest group of patients who received chemotherapy in the UK in 2014 (Chemotherapy Intelligence Unit, 2015)

Toxicity was reported by 116 (35.5%) of colorectal cancer patients, which was very similar to the reporting rate of 530 (35.6%) for the entire population. The mean age of the colorectal cancer patients was 64.5 years (SD=10.6), which was marginally older than that of the whole population of 63.2 years (SD= 11.4). The incidence of colorectal cancer peaks at age 65-80 years (Cancer Research UK, 2015b), so the mean age of the bowel patients in this population was slightly lower. In 2013-14 31% of patients with colon cancer and 42% of patients with rectal cancer had chemotherapy in the UK, which explains why the mean age in this population was slightly lower than the age where bowel

cancer incidence is the highest (Cancer Research UK, 2015a), with Cancer Research UK suggesting that the proportion of patients having chemotherapy is strongly influenced by stage of disease at diagnosis, but age also plays a role in the likelihood of receiving chemotherapy.

The distribution of performance status was similar to the whole population with only one patient performance status 3. This may have been reflective of patients with colorectal cancer or may have been reflective of those patients with colorectal cancer who were considered fit enough candidates for chemotherapy.

The distribution of the intent of chemotherapy in the colorectal cancer patients was similar to that in the whole population and this was as expected from clinical practice where the largest proportion of patients receive palliative chemotherapy compared to adjuvant and neoadjuvant regimens.

As in breast cancer patients, a wide variety of different treatments was used in the colorectal cancer patient group. Only 5 drug classes were seen in the colorectal cancer patients and despite the difficulties with the accuracy of recording, this did probably reflect clinical practice at the time. The grouping of regimens by the number of drugs used, was similar to the whole population, with most patients receiving one or two drugs. This was in contrast to the breast cancer patient group, where significantly more patients received three drugs. The chemotherapy used in the colorectal cancer patients appeared to be much less emetogenic than that given to the whole population and certainly much less than in the breast cancer patients. Again, this reflected what was seen in clinical practice with few highly emetogenic regimens seen and means that treatment was likely to be having a larger effect on toxicity than disease and other variables.

5.4.2.1 Toxicity and Colorectal cancer patients

Multivariable logistic regression analysis of the factors known to affect toxicity in the general population, was applied to the colorectal cancer patients. It yielded pseudo-R^2=0.08, which was actually higher than seen in previous similar analyses for breast cancer patients and the population as a whole, suggesting that for colorectal cancer patients, the analysis explained slightly more of the variance in toxicity, however, it did still leave a significant amount of variance unexplained. Emetogenicity produced a borderline statistically significant prediction (p=0.08), suggesting that those on a moderately emetogenic treatment were significantly more likely to experience a toxicity than those on a low emetogenic treatment. This mirrored what was seen previously in the whole population and the breast cancer patient group. Only 11 (3.3%) patients reported vomiting in the colorectal cancer patient group which was lower than the entire population which had a rate of 89 (5.8%) and nausea was reported by 40 (12.2%) of patients, which is lower than that of the whole population which was 245 (15.9%). It was possible that those in the moderately emetogenic group reported toxicities other than nausea and vomiting, but emetogenicity still appeared to affect the occurrence of toxicity. Further research would be needed to explore this. Chua *et al.* suggested that increasing age increases the risk of grade 3 or higher haematological toxicities (Chua *et al*., 2011) .The review also stated that several trials found that higher performance status increased the incidence of non-haematological toxicity, but this study was unable to prove this. Chua *et al.* also explored the effect of race on toxicity. This was not recorded in this research. No other literature was found that explored toxicity in colorectal cancer patients receiving chemotherapy.

5.4.2.2 Grade of Toxicity in Colorectal cancer patients

The rates of each grade of toxicity reported in the colorectal cancer patients was similar to the rates for the entire study population. A multivariable ordinal regression analysis of the factors shown to affect grade of toxicity for the entire population, found that emetogenicity had a borderline statistically significant effect on the grade of toxicity (p=0.09), with moderately emetogenic

chemotherapy seemingly increasing the grade of toxicity marginally. As emetogenicity increased the risk of toxicity occurring, it followed that it also increased the severity of those toxicities. It may have been possible that the grade of toxicity affected how likely a patient was to report a toxicity, but this was a theory for which no evidence was found and would require more research around reporting methods in order to elucidate it further. The review by Chua *et al.* was the only literature found that looked at the grade of toxicity and the only link found was that increasing age was predictive of grade 3 or higher haematological toxicity but no data was published regarding severity of toxicity (Chua *et al*., 2011).

5.4.2.3 Hospital Admission and Length of Stay in Colorectal cancer patients

There were only 32 patients admitted in the colorectal cancer patient group. This number proved too small to identify any risk factors for admission and thus length of stay. Tracking these patients over a longer period of time or looking at patients treated in other centres would produce a larger number of patients admitted that may result in more meaningful analysis. No data was found in the literature on admission due to chemotherapy toxicity in colorectal cancer patients.

5.4.3 Lung Cancer

Lung cancer patients was the third largest group in the population, accounting for 242 (15.7%) of the population. This was almost in keeping with national statistics which list lung cancer as the third most common cancer in males and females in the UK (Cancer Research UK, 2014). According to Cancer Research UK, in 2013-14, 68% of patients with small cell lung cancer and 25% of those with non-small cell lung cancer received chemotherapy (Cancer Research UK, 2015f). National SACT data reported lung cancer patients as the third largest group of patients who received chemotherapy in 2014 in the UK (Chemotherapy Intelligence Unit, 2015). These would suggest that a large proportion of lung cancer patients do not receive chemotherapy and that is why

it was the third largest group in this research rather than second largest as with national incidence statistics.

Lung cancer incidence peaks in older patients with most cases being seen in 65-79 year olds (Cancer Research UK, 2015f). The mean age in the lung cancer patient group was 67.0 years (SD= 9.1), slightly higher than the mean for the whole population of 63.2 years (SD=11.4).

The lung cancer patient group had a significantly lower proportion of patients who were performance status 0 than the whole population and lower when compared to the breast and colorectal cancer patient groups. The lung cancer patient group also had the highest rate of performance status 3 patients seen. This suggested that the lung cancer patients were less fit than the whole population and less fit than breast and colorectal cancer patients. Lung cancer is heavily associated with smoking, with 72% of cases being caused by smoking (Cancer Research UK, 2015f). It is known that smokers have higher cardiac risk factors and are at risk of a number of other co-morbidities, so it was likely that the lung cancer patients in this research had more co-morbidities than other groups. This could have had an effect on the toxicity reporting as with more co-morbidities it was more difficult to ascertain if the symptoms reported were due to true chemotherapy toxicity or arising from pre-existing conditions. A baseline toxicity assessment would have helped to clarify this.

There was a very high proportion of chemotherapy for palliative intent in the lung cancer patient group than in the whole population and the other disease groups. This reflected the poorer prognosis and survival data associated with lung cancer (Cancer Research UK, 2015f). Significantly less adjuvant and neoadjuvant treatment was seen in the lung cancer patient group and this probably reflected the higher proportion of patients who present with advanced disease that is not curable (Cancer Research UK, 2015f). Surgery for lung cancer is highly invasive with a high mortality and morbidity rate and so is only

suitable for fitter patients (Neal and Hoskin, 2009). Given that lung cancer patients are less fit than others, it would follow that fewer patients received curative therapy.

As with the other tumour sites, a wide range of regimens was used in the lung cancer patient group. Two-drug regimens made up the majority of treatments given to lung cancer patients, and this was quite different to the population as a whole. The majority of regimens were either highly or moderately emetogenic, with very small proportions of low and minimal regimens used.

5.4.3.1 Toxicity in Lung Cancer

A logistic regression analysis for toxicity using the predictors shown to effect toxicity in the other tumour sites yielded no statistically significant results ($p>0.1$). This was unexpected, especially given the high proportion of highly or moderately emetogenic chemotherapy used, which if following the patterns of the whole population or the breast and colorectal cancer patient groups, would have resulted in increased toxicity. This would suggest that either the sample size was not adequate to draw any conclusions from or toxicity was affected by some other factors.

The large meta-analysis by Hardy *et al.* of over 70000 patients with lung cancer, provided a good point of reference (Hardy *et al*., 2010). Hardy *et al.* found that patients on chemotherapy experienced a wide range of toxicities and haematological toxicities were reported as well as non-haematological toxicities. Toxicities were usefully categorised as short term or long term, however short term was defined as within 3 months of chemotherapy, which was very different to the short term toxicities in this research. Reports of nausea ranged from 20.1-60%. An overall short-term adverse effect rate of 1.1-4% was reported, which differed significantly from the 25.2% (61 patients) in this study. It was also significantly less than other rates of reporting, for example in the breast cancer patient group in this research, but also to the

99.1% (740 patients) rate seen in the study by Schonherr *et al.* looking at breast cancer patients receiving FEC chemotherapy. This would suggest that disease and possibly treatment had a big effect on toxicity. (Schönherr *et al*., 2012). The method of data collection in the review by Hardy *et al.* was based around a financial database used for insurance claims, which may have had a large effect on the toxicity reported for economic or financial reasons and the method of identifying toxicity from patient records may not have been robust. The nausea rate reported in the lung cancer patients in this study was 9.9% (24 patients), which was significantly lower than that reported by Hardy *et al*. This suggested that delayed emesis was seen in the studies included by Hardy *et al*. and if this study had followed up patients for longer than a higher rate of nausea may have been seen. It was also possible that the treatments used in this study resulted in less nausea than those in the review by Hardy *et al.*, although this is unlikely as 14 different treatments were used. Hardy *et al*. were only concerned with patients over 65 years of age and in this study, nearly 50% (755) of patients were under 65 years of age, which could suggest that age had an effect of the occurrence of toxicity within a lung cancer patient population. Hardy *et al.* compared the occurrence of toxicity to a group who did not receive any chemotherapy and found a more than two-fold increase in a number of toxicities that were not recorded in this study. This identified a useful control that highlighted toxicities that were due to chemotherapy rather than another reason.

5.4.3.2 Grade of Toxicity in Lung Cancer

The lung cancer patients reported fewer grade 1 and slightly fewer grade 2 toxicities than the whole population. These rates were noticeably lower than in the colorectal and breast cancer patient groups. The numbers of toxicities reported in the lung cancer patient population were too low to perform any meaningful analysis. The review by Hardy *et al.* did not focus on the severity of toxicity (Hardy *et al*., 2010), so no literature was found to explore this further.

5.4.3.3 Hospital Admission and Lung Cancer

In the multivariable logistic regression of admission, no significant predictions were found ($p>0.1$), but the lung cancer patients did appear to have a higher admission rate than the other tumour sites and than the whole study population. The median length of stay for lung cancer patients was shorter than for the whole population, which could suggest that lung cancer patients had toxicities that were more easily treated as an outpatient. When looking at lung cancer patients independently, the sample size was too small to allow for a meaningful logistic regression analysis to be developed. This area would require more research as no literature was found regarding the risk of hospital admission in lung cancer patients specifically on chemotherapy, although Cuppens *et al.* looked at admissions in lung cancer patients (Cuppens *et al*. 2016).

5.5 Individual Toxicities

The three most commonly occurring toxicities were explored as individual secondary outcomes, in order to identify predictors of toxicity, severity of toxicity, hospital admission and length of stay. It was hypothesised that rates of reporting of the individual toxicities would follow the patterns of toxicity as a whole and this was found to be partly true. The same was partly true for grade of toxicity and for admission and length of stay.

5.5.1 Nausea

Nausea and vomiting are closely related and vomiting often follows nausea (Hesketh, 2008). They were treated as separate variables in this study in order to understand the factors that influenced them.

Nausea was the most commonly reported chemotherapy toxicity and it is well-known that nausea can be a troublesome side effect of chemotherapy that is commonly feared and experienced by patients (Janelsins *et al*., 2013). The patients who reported nausea were separated out in SPSS® and analysed as a sub-population.

This research was concerned with only acute nausea, which was reported by 245 (15.9%) of patients. This rate seemed lower than those reported by Ihbe-Heffinger *et al.* of 32.8% (68 patients) (Ihbe-Heffinger *et al*., 2004), Lindley *et al.* of 56% (68 patients) (Lindley *et al*., 1992), Pirri *et al.* of 62% (123 patients) (Pirri *et al*., 2011) Escobar *et al.* of 42% (101 patients) (Escobar *et al*., 2015) and Kottschade *et al.* of 35% (145 patients) (Kottschade *et al*., 2016), however none of these studies had a similar population to this research and several of them reported nausea and vomiting as one entity rather than two separate symptoms. Many of the studies only included patients with a single diagnosis or age group. It should also be pointed out that most of these studies did not differentiate between acute and delayed CINV, which could have increased the percentage reported to have experienced nausea.

The mean age of those patients experiencing nausea was slightly lower than that of the entire study population, but the distribution of age in the patients experiencing nausea is similar to that of the whole population and the differences in rates of nausea between the age groups was not found to be significantly different. Only Hesketh and Kottschade *et al.* suggested that age was a risk factor for nausea with chemotherapy, however Kottschade *et al.* only looked at highly emetogenic chemotherapy, so could not be applied to a whole chemotherapy population (Kottschade *et al*., 2016) (Hesketh, 2008). Hesketh quoted three references supporting the statement that younger patients were more likely to experience CINV, all of which only looked at cisplatin based treatments, which are known to be highly emetogenic (Hesketh, Kris, Basch, Bohlke, Barbour, Clark-Snow, Danso, Dennis, Dupuis, Dusetzina, Eng, Feyer, Jordan, Noonan, Sparacio, Somerfield and Lyman, 2017a). As such no reliable data was found linking nausea to age, in a general population receiving a variety of treatments.

Performance status appeared to have an effect on nausea, as a significantly higher proportion of patients who were performance status 0 reported nausea than in the other performance status groups and a Pearson's χ^2 test suggested that this was statistically significant ($p<0.01$). However in the multivariable logistic regression analysis, performance status did not yield any statistically significant predictions ($p>0.1$). Pirri *et al.* suggested functioning status as a risk factor for CINV (Pirri *et al*., 2013), but no other literature was found that linked performance status to nausea. It was therefore not possible to confirm if performance status increased the risk of nausea, despite other patient factors such as history of motion sickness, having been shown to be predictive of CINV (Kottschade *et al*., 2016). This suggested that patient factors can increase the risk of nausea but this research was not able to further explore this theory.

It was expected that the intent of treatment would have an impact on nausea, but as stated previously the intent of treatment may have been affected by other variables such as treatment used and disease treated. Neoadjuvant patients experienced a higher rate of nausea than the other groups, with the palliative group experiencing the least. This appeared significant using a X^2 test ($p<0.01$) but did not produce any statistically significant predictions in the multivariable regression analysis. It may have been expected that the more intense a treatment, the more nausea may be seen, but no literature was found that explicitly described the effect of the intent of treatment.

The disease being treated may have had an effect on nausea, although the numbers of patients in each group was not evenly distributed and so made comparison difficult. Breast, CNS and upper GI cancer patients reported the most nausea. It was possible that nausea was a symptom of some of the diseases and it was not possible from the research to identify what nausea was due to chemotherapy and what was due to other causes such as disease. Of course, as seen previously, the disease being treated will have involved interaction with a number of other variables including treatment and treatment intent. In the regression analysis, no statistically significant predictions were produced. Kottschade *et al.* suggested that a diagnosis of breast cancer increased the likelihood of CINV on day 1 but this could not be corroborated by this research (Kottschade *et al*., 2016). This research was also unable to identify a clear link between disease and nausea.

It was expected that treatment would have a significant effect on nausea as trials for individual agents or regimens will all report slightly different rates of nausea and the fact that a classification system is in place, which describes the risk of nausea associated with a given treatment, confirms that treatment is likely to have a large effect on nausea (Hesketh *et al.* 2017a). Indeed the pathological mechanisms of CINV have been documented and the different mechanisms for different drugs explained. When treatment was grouped according to cytotoxicity ($p<0.01$), number of drugs ($p<0.01$), emetogenicity

($p<0.01$) and commissioning status ($p=0.01$), the differences between the nausea in the groups appeared statistically significant by χ^2.

Multivariable logistic regression confirmed that nausea increased as the number of drugs increased. Surprisingly the analysis did not identify any statistically significant links between nausea and the emetogenicity of an agent ($p>0.1$). This highlighted a problem with the data as it was well-documented that the emetogenicity of a treatment affects the likelihood of nausea (Basch, Hesketh, *et al*., 2011). It was likely that the sample size of patients who experienced nausea was not large enough to produce reliable statistics. As such, patients would need to be followed up for longer to identify any delayed nausea and to produce a larger sample size, perhaps with patient demographics more controlled to allow for comparisons between groups. Hesketh suggested that female patients and younger patients were at a higher risk of CINV (Hesketh, 2008). This research was unable to confirm this, as gender was not recorded and the data did not support a link between age and nausea. Hesketh also stated that patients with a high pre-treatment expectation of severe nausea were more likely to experience nausea after treatment. This was not recorded in this research and so could not be confirmed. Hesketh also stated that chemotherapy dose and emetogenicity were predictive factors of nausea. Dose of chemotherapy was not explored in this research.

5.5.1.1 Grade of Nausea

No significant differences were found in the grade of nausea using the factors expected to affect severity of nausea. Ordinal logistic regression analysis did not show any statistically significant predictions with respect to grade of nausea ($p>0.1$). It was also difficult to find much in the literature regarding the severity of nausea. Nausea is a subjective symptom and so there may have been distinct differences in reporting between patients, however little literature was found that explored this.

5.5.1.2 Hospital Admission and Nausea

The rate of admission in the patients who reported nausea was very similar to the admission rate in the population as a whole, with median length of stay being slightly lower. No significant data was found that linked nausea and admission rate or length of stay. This was also an area not covered in the literature as very little data was found. Only Ihbe-Heffinger *et al.* reported on hospital admission, and that study only found 1 admission (Ihbe-Heffinger *et al*., 2013). It was seen in this research that there were 20 admissions for nausea and vomiting, suggesting that it was an issue, but perhaps this study was not powered to make any predictions regarding the risk factors.

5.5.2 Vomiting

As described above, chemotherapy induced nausea and vomiting was frequently described in the literature as a single entity rather than two separate toxicities. However, vomiting was the second most reported toxicity, affecting 89 (5.8%) of patients, so it was thought worthwhile to explore it in more depth. As with nausea, the rate of vomiting was significantly lower than rates quoted in the literature, but all of the literature reviewed included acute and delayed vomiting rather than just the acute that was included in this study. Escobar *et al.* quoted separate rates for nausea and vomiting and suggested a rate of 20.8% (100 patients) for vomiting in patients receiving moderately emetogenic chemotherapy (Escobar *et al*., 2015). This included delayed and acute vomiting, suggesting that delayed vomiting accounted for a significant proportion of vomiting reported when compared to this study.

The mean age of patients reporting vomiting was lower than that of the rest of the population. This would support the suggestion by Hesketh and Kottschade *et al.* that younger age was predictive of CINV (Hesketh, 2008; Kottschade *et al*., 2016), however those studies included delayed CINV. The distribution of age in patients reporting vomiting looked similar to the age distribution in the whole population. The rate of vomiting was highest in the youngest age group and the differences between the groups were significant ($p<0.01$), but the

number of patients reporting vomiting was quite low. The statistically significant Spearman's correlation coefficient of -0.081 (p=0.02) suggested that as age reduced, vomiting rate increased, which, again, would agree with Hesketh and Kottschade *et al*.

Although vomiting appeared to be higher in the lower performance status groups, the numbers of patients in each group was not evenly distributed making direct comparison difficult, with the χ^2 test showing that the variance was not statistically significant ($p>0.1$).

As with nausea, vomiting was highest in the neoadjuvant patients, but where nausea was lowest in the palliative patients, vomiting was lowest in adjuvant patients. The χ^2 test suggested that the differences between the groups were significant, but the regression analysis was unable to make any statistically significant predictions. It was unclear why the nausea and vomiting rates were different in these groups and further research with a larger sample size would be needed to further explore this. If patients had been followed up for longer, and data collected on delayed nausea and vomiting, it may have been possible to draw further conclusions.

The disease being treated seemingly affected vomiting in the same way as it affected nausea, with CNS, breast and upper GI cancer patients reporting the most. This might have suggested that these patients were pre-disposed to vomiting or there may have been other factors within the disease groups such as treatment or treatment intent that were affecting the rate of vomiting. Again, the multivariable logistic regression analysis was unable to confirm the effect of disease on vomiting rates.

It was anticipated that the treatment used would have a large effect on vomiting, as with nausea. When grouped according to commissioning status, cytotoxicity and drug class, there were no statistically significant differences

seen between the groups ($p>0.1$). When grouped according to the number of drugs, vomiting increased significantly, the more drugs used. A Spearman's correlation coefficient of 0.184 ($p<0.01$) suggested a positive correlation, as seen with nausea. No data was found in the literature to support this, although it is known that dose can affect CINV and so it may follow that the additive toxicities of different agents can increase the risk of vomiting (Hesketh, 2008). It is known that some agents have an additive effect, for example anthracycline/cyclophosphamide combinations are more emetogenic than the single agents (Hesketh, Kris, Basch, Bohlke, Barbour, Clark-Snow, Danso, Dennis, Dupuis, Dusetzina, Eng, Feyer, Jordan, Noonan, Sparacio, Somerfield and Lyman, 2017b). This could not be confirmed in the regression analysis. As expected, vomiting rates were highest in the highly emetogenic chemotherapy group. Again, regression analysis could not confirm this, but the differences between the groups was significant according X^2 ($p<0.01$).

5.5.2.1 Grade of Vomiting

Ordinal logistic regression analysis revealed no statistically significant predictions around the grade of vomiting ($p>0.1$). As the number of patients reporting vomiting was fairly low, it was likely that the sample size was not adequate to identify statistically significant links between grade of vomiting and the predictors. Unlike nausea, the differences between the age groups of the patients who experienced vomiting were statistically significant according to Kruskall-Wallis ($p<0.01$). The youngest group of patients reported the highest grades of vomiting. No literature was found that explored the severity of vomiting, so comparison was not possible. No other predictor showed a statistically significant link with grade of vomiting ($p>0.1$). This could be an area of interest for future research, as more severe nausea or vomiting may have implications for patients and the health economy. A larger sample size and data including delayed vomiting would be required to explore this further.

5.5.2.2 Vomiting and Admission and Length of Stay

Only 14 patients who reported vomiting were admitted, meaning that there was not sufficient data to perform meaningful analysis, and this was not something that was explored in the literature, again making it an area of interest for future research.

5.5.3 Fatigue

Fatigue was the third most reported toxicity. Fatigue is a subjective variable and the reporting in this research was in accordance with CTCAE criteria (National Cancer Institute, 2010), which was a very crude measure and not particularly descriptive. From the literature, it was clear that consensus did not exist as to a standardised tool for reporting, assessing or describing fatigue (Hauser *et al*., 2008). As no baseline assessment of fatigue was undertaken, it was not possible to definitively say if the fatigue reported was due to chemotherapy. It was possible that disease, co-morbidities or other factors could have resulted in fatigue.

The rate of fatigue reporting was significantly lower than those seen in the literature (Servaes *et al*., 2008). This was probably explained by the short period of time between chemotherapy administration and toxicity assessment. All of the trials reviewed assessed fatigue over a much longer period. This study only considered first cycle chemotherapy and so it was possible that further cycles of chemotherapy had a cumulative effect on fatigue.

The mean age of patients who reported fatigue was slightly lower than the whole population and the distribution of age in those patients experiencing fatigue looked similar to that of the whole population. No statistical difference was found between fatigue rates in the different age groups ($p>0.1$) and this was in agreement with the literature as no studies were found that linked age to fatigue.

No link was found between performance status and fatigue. Although fatigue was linked to comorbidity in the literature (Barnes and Bruera, 2002), no studies were found that explicitly looked at performance status as a predictor. Hauser *et al.* linked fatigue with poorer performance status, but this was as an outcome rather than a predictor (Hauser *et al*., 2008).

There was also no statistically significant difference in the fatigue rates between treatment intent groups ($p>0.1$). Much of the literature around fatigue focussed on advanced cancer, which would suggest chemotherapy of palliative intent was used. Barnes and Bruera stated that treatment is thought to contribute to fatigue, but did not go in to detail regarding treatment intent (Barnes and Bruera, 2002). There was much data to suggest that advanced cancer itself causes fatigue (Cramp and Bryon-Daniel, 2012; Barnes and Bruera, 2002; Hauser *et al*., 2008), but also data from other studies confirming that chemotherapy can cause fatigue (Servaes *et al*., 2008). It could then be that there was an additive effect in terms of fatigue, in patients on chemotherapy for advanced cancer, however no data was found to support this.

The literature elucidated cancer related fatigue as an accepted concept and as such it was expected that there would be a difference in fatigue rates between the different diseases. Indeed, rates were different between the diseases with breast cancer patients having the highest rate of fatigue. The numbers in the groups were quite different, meaning that size-effect could not be ruled out, and despite χ^2 giving $p=0.05$, regression analysis was unable to show any difference between the disease groups. Other variables would automatically be introduced when dividing fatigue rates by disease, for example breast cancer patients received the highest proportion of adjuvant and neoadjuvant treatment. Data was found in the literature linking fatigue with different types of cancer, but no studies were seen that compared fatigue rates between different diseases. It was difficult to know what was cancer related fatigue and what

fatigue was due to chemotherapy. A baseline assessment of fatigue would have helped to explain this. The rates of fatigue in this study were significantly lower than in the literature, with one study quoting fatigue rates in cancer patients of up to 99% (Barnes and Bruera, 2002). This was probably due to the fact that this study only focussed on acute toxicity. It was probable that if patients had been followed up for longer, higher reporting rates of fatigue would have been seen.

From the literature, it was anticipated that the type of treatment would have a major impact on the occurrence of fatigue. Little literature was found that compared fatigue rates between different treatments. When grouped according to cytotoxicity ($p<0.01$), number of drugs ($p<0.01$) and commissioning status ($p<0.01$), fatigue rates were statistically significantly different between the groups. Regression analysis confirmed that cytotoxic chemotherapy was significantly less likely to be associated with fatigue than those on a mixed regimen. Those on non-cytotoxic chemotherapy were the least likely to experience fatigue. This could have been explained by an additive effect on toxicity of using a combination of drugs. It should be noted that the numbers in each group were significantly different, so size effect was likely. Also, this interacted with the number of drugs variable, as patients in the mixed group would be receiving >1 drug. As seen with other toxicities, the higher the number of drugs, the more likely fatigue was to be seen. This also could have been explained by an additive effect, possibly with different agents inducing fatigue via differing mechanisms. The effect of number of drugs on fatigue could not be confirmed by the regression analysis. The other factor found to predict fatigue was the commissioning status of a drug. Those on cancer drugs fund funded drugs experienced a significantly higher rate of fatigue. The size of these groups was vastly different and so size-effect was highly likely. The other means of grouping the treatments did not yield any statistically significant differences.

5.5.3.1 Grade of Fatigue

Grade of fatigue did not appear to be affected by any of the predictors in an ordinal logistic regression analysis. No data was found in the literature around the severity of fatigue and so no comparisons could be made. As the number of patients reporting fatigue was fairly small, the numbers in each of the various groups was also small, making it difficult to draw reliable conclusions. The effect of age on the grade of fatigue was unclear. The differences between the age groups was statistically significant ($p<0.05$), but there did not appear to be any pattern to the proportions of patients complaining of each grade of fatigue.

It was seen that the higher the performance status, the higher the proportion of patients reporting fatigue, with the inverse being true for grade 1 fatigue. This agreed with Hauser *et al.*, who suggested that fatigue was associated with higher performance status. It was not known if the fatigue resulted in the higher performance status, or if the poorer functional state resulted in the fatigue (Hauser *et al*., 2008). It was not possible to identify from this data, if the reported fatigue was a result of disease, co-morbidities or cancer treatment and again, a baseline assessment of fatigue would have helped to clarify this.

The numbers in the groups when fatigue severity was compared between the different treatment intents were too wide to draw any conclusions from. Disease and treatment grouped according to cytotoxicity, number of drugs, drug class and emetogenicity did not appear to have any effect on the grade of fatigue ($p>0.1$). When grouped according to commissioning status, CDF patients had a higher rate of grade 2 fatigue than baseline commissioning patients, but this could not be confirmed in the regression analysis. The significance of this was unclear, as it was a very broad way of grouping the treatments, but may have been of interest considering the controversial nature of the CDF (Aggarwal *et al*., 2017).

5.5.3.2 Admission and Length of Stay and Fatigue

Only 26 admissions were seen in patients complaining of fatigue, which accounted for 16.4% of those patients, higher than the admission rate in the wider study population. Only 2 patients were admitted due to fatigue or weakness. It was possible that fatigue contributed to other reasons for admission. As Ryan *et al.* explained, fatigue is often associated with other conditions such as anaemia and cachexia, which could have contributed to hospital admission rates (Ryan *et al*., 2007). Median length of stay was shorter than that of the whole population, but the number of patients involved made it impossible to undertake any meaningful analysis. There was no data found in the literature around fatigue and admission or length of stay.

5.6 Economic Effects of Hospitalisation

Assessing the financial cost of admission from toxicity proved difficult. A national tariff was available at the time of writing, covering hospital admission in England (NHS Improvement and NHS England, 2017). Each admission attracted a different tariff depending on the investigations and interventions undertaken in that admission and based on the complexity of the care required. This made identifying a cost of admission due to chemotherapy toxicity difficult, as each individual case would attract a different tariff. For example, in the national tariff workbook, there were 11 possible codes for a sepsis care episode and 4 codes for fever of unknown origin. Many chemotherapy patients would be admitted with fever and some with neutropenic sepsis, even with this specific reason for admission, there was not one clear tariff that would apply, in order to assess the economic impact of admission. Without that detail, it was still possible to say that admission to hospital was a cost pressure to the health economy and the ability to predict and reduce toxicity and subsequent admission, would be financially beneficial to the health economy. In order to explore this further in this study population, it would be necessary to investigate each individual admission and assess how it was coded. This would have to be done at patient level and was too time consuming to be undertaken in this study, but is an area that further research could focus on. The lack of available literature regarding the economic impact of chemotherapy toxicity and hospital admission, suggested that this was an area that was not well understood and was not an area that this research was able to add to. Some studies were found that looked at the cost of admission in specific diseases, but none looked at a whole chemotherapy population (Latremouille-Viau *et al*., 2017; Irwin *et al*., 2016; Paessens *et al*., 2011). Mean costs of admission were quoted and were fairly similar in each study, however none of the data was from UK patients and admissions within the NHS.

5.7 Implications for Practice

The findings of this research may have various implications for practice, as well as identifying areas for future research as described above. The literature showed that toxicity was generally felt to be a negative phenomenon with implications for the patient and the healthcare system. As such there are potential implications for the patient and the healthcare system:

- Implications for the patient
    - Knowledge of the likelihood of toxicity occurring or the potential severity of toxicity may influence decisions around proceeding with chemotherapy treatment. An example may be in adjuvant chemotherapy where the potential benefit to survival may be relatively small (Neal and Hoskin, 2009)
    - Knowledge of the likelihood of toxicity occurring or the potential severity of toxicity may influence choice between different treatments when more than one option is available
    - Knowledge of the likelihood of a hospital admission due to toxicity may influence treatment choice, for example patients who have caring responsibilities may choose not to undertake a treatment that is more likely to result in an admission
    - Greater element of control for patients around treatment decisions and planning ahead when undergoing treatment

- Implications for the healthcare provider
    - Greater knowledge of the likelihood of toxicity, hospital admission and length of stay allows for better planning of services required to respond to the needs of patients in terms of :
        - Financial planning
        - Capacity planning
        - Resource planning
        - Education of workforce
        - Forward planning when introducing new treatments or evaluating existing treatments
    - At NUH, this will allow the CATT team to develop evidence-based interventions to target patients most at risk of toxicity and hospital

admission. It may be that certain groups of patients would benefit from further telephone calls and supported self-management of toxicities. A review of the service could decide where to focus the resource so that it provides the best possible service to patients. Ongoing data collection will allow for further analysis in the future and continual review of the service

Further research would be required to further validate the findings of this study, with a multi-centred approach and larger numbers of patients, following patients up for longer. This could aim to produce and validate a prediction tool for toxicity and subsequent admission, which would provide a robust estimation of toxicity and admission risk and further ratify the implications for practice mentioned above.

5.8 Limitations

Due to time constraints and difficulty obtaining the data, it was not possible to review deaths within 30 days of chemotherapy in this study. Death data is collected in a separate system in the trust and cause of death as stated on death certificates does not make it clear if a chemotherapy toxicity was responsible for the cause of death or if another cause was implicated. As such death data was not collected and was omitted from the research. Mortality is an important factor in terms of chemotherapy as any drug carries an element of risk and the clinician needs to be sure that the risks of chemotherapy are out-weighed by the potential benefit. Death within 30 days of chemotherapy was the interest of the 2008 NCEPOD report, which made various recommendations to ensure that decisions to use chemotherapy fully assessed the potential risk of its use (Mort *et al*., 2008). These recommendations have been embedded into practice at NUH, with any death within 30 days of administration of chemotherapy, warranting discussion at the monthly morbidity and mortality meeting. The meeting aims to review practice and identify and share any learning points for the future.

5.7.1 Methodology Limitations

It was acknowledged that the methodology had a number of limitations. Gender was not collected as part of the call back service and as such could not be included in any data analysis. The possibility of gender being a predictor of toxicity or hospital admission could not be included in this research.

As alluded to previously, this study was only able to explore acute chemotherapy toxicity within the first 24 hours following the first cycle of chemotherapy. The call back service was only able to provide one telephone call per patient and as such no data could be collected on any later toxicities that may have occurred prior to the next cycle. This was in contrast to all of the literature that was reviewed, most of which collected toxicity data for the duration of a treatment. In order to draw true comparisons, this study would have had to continue to collect toxicity data for the duration of treatments, but

this would have been extremely labour intensive for a population of the size seen in the study and the time and resource required to do this were not available. The time period of the telephone call also meant that for many oral regimens, steady state may not have been reached, so the full extent of toxicity was unlikely to be seen.

Only the first cycle of toxicity was included in the data. It was possible that toxicity may have changed as patients progressed further through chemotherapy, with some toxicities occurring as a cumulative effect of subsequent cycles of chemotherapy. This was beyond the reach of the data in this study, although if a similar methodology was applied prior to subsequent cycles of chemotherapy, it would allow for analysis of such effects on toxicity.

Stage of disease was not recorded in the data of this study, meaning that within each disease group there were many variations of the same disease. Some disease that is localised to a non-visceral area, may have been unlikely to produce significant symptoms, whereas metastatic disease affecting a number or organs, may have produced significant symptoms and affected functioning, thus affecting toxicity and admission rates.

Outcomes of toxicity were recorded as free text by the nurses, however not explored in this study. The outcome recorded would have been the outcome at the time of the telephone call. This could be a referral to another healthcare provider, advice for self-management or hospital admission. This would not elucidate the true effect of a toxicity as this effect could be felt well beyond the initial 24 hours after chemotherapy.

There were 37 different reasons for admission within 30 days of chemotherapy. As such it was very difficult to draw any conclusions, as numbers for each admission were so small. It was also impossible to be certain that the

admission was due to a chemotherapy toxicity, as many of the symptoms could have been due to other causes such as disease.

This study looked at the occurrence and severity of toxicity as well as hospital admission and length of stay, but did not extend to the consequences of any of these. It was assumed that toxicity was a negative experience for the patient and detrimental to their overall wellbeing. Kalsi *et al.* suggested that toxicity was responsible for dose reduction, discontinuation and even death (Kalsi *et al*., 2014). Further research would be warranted in to the effects and outcomes of patients experiencing toxicity.

Toxicity can be a subjective outcome and although a nurse-led toxicity assessment was performed, the data collected still relied on patients reporting the toxicities. Different patients may have rated toxicities differently. The CTCAE criteria (National Cancer Institute, 2010) should have minimised the patient bias in this, but it could not be completely excluded as a potential factor for some variance. What was severe for one patient may have been mild for another. A particular example of this would be fatigue. Jenner *et al.* showed that patients had a high rate of reporting toxicity when asked to complete questionnaires (Jenner *et al*., 2010), however this study did not have a comparator and no literature was found that compared toxicity rates in patients asked to complete structured self reporting of toxicity with standard of care. It is likely that different centres have different means of assessing and recording toxicity and so comparison could be difficult. Further research would be required to further explore this and to elucidate the effect of reporting models on toxicity.

The study did not include a baseline assessment of toxicity symptoms, prior to the first cycle of chemotherapy. It was therefore possible that some patients may have already been experiencing the toxicity symptoms caused by other factors such as disease, prior surgery or co-morbidity. It was not possible to

conclude from this study that the symptoms experienced were definitely a direct result of the chemotherapy treatment.

Haematological and non-patient reported toxicities were not included in the research as they were not collected. Haematological toxicity is a common consequence of chemotherapy (Chua *et al*., 2011), but in order to collect data on this, a significant investment of resource would have been needed to review and record blood count results over a prolonged period of time. Other effects such as impairment of renal or liver function or electrolyte disturbances were not assessed in this research.

6.0 Conclusion

The research aimed to identify the factors influencing the occurrence and severity of acute chemotherapy toxicity along with the likelihood of hospital admission, which was partly achieved. It focussed on a whole patient population of patients with a solid tumour treated with chemotherapy in a large UK teaching hospital trust. In order to do this, a dataset of toxicity assessment 24 hours following the first cycle of chemotherapy was produced and analysed. The methodology had known limitations but was able to address the initial research question. This study was felt to be unique as nothing similar was seen in the published literature, although studies looking at similar questions were found, none used an identical population.

A heterogeneous population was studied, which had a wide age range and range of performance statuses. Chemotherapy of all treatment intents was studied and nearly all cancer types were included in the analyses, although small numbers in some groups meant that they had to be excluded. A wide range of treatments was used and it was necessary to group these by several different mechanisms.

Overall incidence of toxicity was found to be 35.6% (530 patients), which was comparable to other studies seen in the literature. The incidence of hospitalisation due to chemotherapy toxicity within 30 days of the first cycle was found to be 13.1% (203 patients). The incidence of death due to chemotherapy toxicity could not be established due to difficulties in collecting the data.

Factors affecting the occurrence of toxicity were identified. The disease being treated was found to influence toxicity, with breast and upper GI cancer patients more likely to experience a toxicity than other tumour sites. It was acknowledged that there was potential overlap of the predictors and this could be especially evident with disease. Age and treatment intent were found not to

affect the occurrence of toxicity. Initial findings suggested that performance status had an effect on toxicity, this was not proved in logistic regression analysis. When treatment was grouped according to the number of drugs used in the chemotherapy regimen, regression analysis suggested that the more drugs given, the higher the rate of toxicity. It was not possible to prove an effect on toxicity of the emetogenicity of a regimen, this was thought to have a relationship with toxicity, but was possibly confounded by other variables or there was a type I error in the data.

Factors affecting the severity of toxicity were identified using descriptive statistics to highlight any possible relationships and ordinal logistic regression analysis to assess these relationships further. Disease was the only factor that was found to predict the grade of toxicity with urology, gynaecology and lung cancer patients all being associated with higher grades of toxicity. It was suspected that age and performance status had an effect on the grade of toxicity, although this data was not able to prove this when multivariable regression was performed.

The risk of hospitalisation due to chemotherapy toxicity within 30 days of chemotherapy was explored using multivariable logistic regression analysis. The likelihood of admission was found to be affected by the disease being treated, with patients with head and neck, upper GI and lung cancer having a higher risk of admission than other tumour sites. The number of drugs given also had an effect on the risk of admission with patients on three drugs having a higher likelihood of being admitted. Age and performance status appeared to have a relationship with the risk of admission in descriptive statistics and univariate regression analysis, but multivariable regression was unable to explain these links.

Length of stay appeared to reduce as age increased with a statistically significant correlation ($p=0.04$). Intent of treatment, the number of chemotherapy drugs in a regimen and emetogenicity all appeared to have an

effect on length of stay. Due to complexity of the data and limitations to the methodology, it was not possible to undertake regression analysis to confirm the effect of the predictors on length of stay.

Sub-group analyses of breast, colorectal and lung cancer patients, used the same regression analysis as in the whole study population and showed that in breast cancer patients, the use of 3 drugs increased the risk of toxicity occurring and in colorectal cancer patients the use of moderately emetogenic chemotherapy increased the incidence of toxicity. Admission rates in breast cancer patients was lower than the whole population, similar in the colorectal cancer patients and higher in the lung cancer patients Length of stay was shortest in the lung cancer patients and similar to the study population in breast and colorectal cancer patients.

The 3 commonest toxicities seen were nausea, vomiting and fatigue and these were analysed as secondary outcome measures using the same regression analysis as in toxicity. The analyses showed that the risk of nausea was increased as the number of chemotherapy drugs given increased. The same was true for vomiting. The number of drugs also had an effect on fatigue, with those on 1 drug being less likely to experience fatigue. Admission rates for patients with nausea and fatigue did not differ from those patients who did not report these toxicities and the admission rate for vomiting did not show a difference that was statistically significant ($p>0.1$).

The complexity of NHS financial systems meant that it was not possible to develop an analysis that could accurately estimate the economic effects of toxicity.

Further research is warranted into chemotherapy toxicity, as the effects can be detrimental to the patient and a burden on the health economy. Toxicity assessment over a longer time period or larger patient group would further add

to the body of evidence around this. Hospital admission due to chemotherapy toxicity is an under-researched area and would benefit from a large, multi-centre study to analyse the factors that affect the likelihood of this sequela of chemotherapy use.

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Appendix 1

Chemotherapy Ring-back Service

Standard Operating Procedure

1. Obtain the list of patients to call that day from the report produced by Chemo care, sent to the Admission avoidance team email

2. Open the patient's Chemo care record and familiarise yourself with the regimen. If necessary, look for the appropriate Macmillan information sheets in the relevant folder of the shared drive.

3. Check that chemotherapy was given and a ring back is necessary. If needed, the day when a ring back is required for each regimen can be found in the "days of ring back" spread sheet in the admissions avoidance shared drive. Note that some regimens have two ring backs.

4. Open the correct database from the "Database and clinical info" folder in the shared drive. Ensure that the database matches the regime prescribed on Chemocare

5. Record the patient's initials in the "patient details" column of the database and complete columns B to H.

6. Obtain the patient's telephone number from NotIS and place the call.

7. Confirm that you are speaking to the patient. Patients can only be discussed with a relative with the consent of the patient.

8. After introducing yourself, ask the patient how they are and how they have found the chemotherapy. Use open questions to begin with, then move on to specific toxicities. For each toxicity, record the grade and the outcome. Ensure you get details of:

    a. Any fever
    b. Nausea
    c. Vomiting
    d. Stomatitis
    e. Diarrhoea
    f. Constipation
    g. Lethargy
    h. Anorexia
    i. Dyspnoea
    j. Rash
    k. Neuropathy motor
    l. Neuropathy sensory
    m. Bleeding
    n. Arthralgia

o. Bruising
p. Extravasation
q. Anything else the patient discloses

9. Offer advice as appropriate on self- care and consider the need for further assessment. Ensure that the patient knows how to correctly take any supportive care.
10. Consider arranging a further phone call the next day if there are concerns about any symptoms.

11. Record all of the toxicities in the relevant database using the drop down boxes.

12. Ensure that the database is saved – please note that only one person at a time can access each database so please ensure that it is closed when finished.

13. Find the patient record on NotIS and using medical office – complete a letter to the GP. Ensure that you include any details of toxicities experienced and the advice given. Include any other info that you feel may be relevant.

14. Copy the letter on medical office and paste it into the annotation section of the patient's Chemocare record.

15. Make a note of when you feel a further ringback is required. This may vary patient to patient.

Appendix 2

Data items collected as part of the Chemotherapy ring back service

- Date of call
- Name, hospital number, date of birth (removed for research purposes)
- Chemotherapy regimen
- Cancer diagnosis
- Intent of chemotherapy
- Cycle number
- Day of treatment cycle (eg Day 1, day 8)
- Performance status at time of chemotherapy administration
- Toxicity review – the following toxicities are assessed and the grade recorded along with any advice given:
    - Nausea/vomiting
    - Stomatitis
    - Diarrhoea past 24 hours
    - Constipation
    - Lethargy
    - Anorexia
    - Dyspnoea
    - Rash
    - Neuropathy – motor
    - Neuropathy – sensory
    - Bleeding
    - Arthralgia/pain
    - Bruising
    - Extravasation
    - Other

Appendix 3

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APPLICANT'S ETHICS CHECKLIST

This checklist is designed to help you to decide whether or not ethics approval is required and, if required, to decide on the appropriate ethics review procedure –
please read Annex 1 on page 5 before you complete this form

Please Note:

a) This Checklist should be completed for all research projects involving human participation, human biological material or human data.

b) All questions on this checklist should be completed.

c) Contact details (email address) should be given for PI or PS and student (if applicable).

d) In the case of Student projects, Supervisors should read and sign this checklist (in the correct box – EITHER/OR – not both boxes) BEFORE it is submitted to the Ethics Administrator for sign off by the Chair of the Research Ethics Panel.

e) Guidance on the 2 different ethics review procedures that together make up the University's Ethics Review System (i.e. 'University' and 'NHS') is available on the University Ethics website.

f) If your project will involve human tissue/biological fluids you should contact the UoB Designated Individual for the HTA licence, Dr Sue Boyce for advice (s.g.boyce@bradford.ac.uk or on 01274 235879)

g) **If this Checklist is NOT correctly completed, it will be returned to you unauthorised.**

Project Title: Assessing the risk of Chemotherapy toxicity and hospital admission due to toxicity

Name of Principal Investigator / Principal Supervisor: Dr J Silcock / Dr E James

Contact Details – email address J.Silcock@bradford.ac.uk
Eleanor.James@nuh.nhs.uk

Department/School Pharmacy, School of Life Sciences

Name of Student (if applicable**): Samuel Malton**

Contact Details – email address Samuel.malton@nuh.nhs.uk

Has the Principal Investigator / Principal Supervisor attended appropriate ethics training?

Yes ☐ No ❒

Has the student attended appropriate ethics training? Yes ❒ No ☐

Please give summary of project (max 150 words**):**

At Nottingham University Hospitals, a new service has been established involving a nurse led call back service to all oncology patients receiving chemotherapy. Patients receive a call back 24 hours after their first cycle of chemotherapy and undergo a full toxicity assessment over the telephone. Data is collected around toxicity, which will be used to look at the factors that can be used to predict chemotherapy toxicity and the risk of hospital admission from toxicity.

Q1	**Is the proposed project an <u>empirical research</u> project involving people?** • Will the project include primary data collection from human participants, their data or their tissue? • Will it constitute an 'investigation undertaken in order to gain knowledge and understanding'? (This includes work of educational value designed to improve understanding of the research process.) If you answer 'Yes' to Q1 ethical approval may be required, move to Q2. If you answer 'No' to Q1 then a research ethics review is not usually required; please move to question 1a. ***Note**: there may be occasions where a project is not defined as research but still raises ethical issues – please submit for review if this is the case.*	Yes ☐ No ❒ Yes ☐ No ❒ Yes ☐ No ❒
Q1a	**Is the proposed project an audit or service evaluation involving humans?** A more detailed definition of Research, Audit and Service Evaluation is available on the University Ethics website. If you consider that ethical review is not required, please explain briefly why not, below: The only data used in the study will be that that is collected as part of the chemotherapy service at Nottingham University Hospitals. Data is not being collected solely for the purpose of research. It is part of the student's role to be involved with the service and the student would have access to the data as part of that role even if research were not being undertaken.	Yes ☐ No ❒
Q2	**Will the research project involve the <u>NHS</u>?** e Research Ethics and Governance in NHS and Social Care page he website If you answer 'No' to Q2 move on to Q3 If you answer 'Yes' to Q2 ethical approval will be required by NHS Research Ethics Committee (NREC). Please submit your	Yes ☐ No ❒

	approved NREC application with this checklist before commencing the work.	
Q3

Q5	**Will the research project involve <u>human tissue (but not requiring NHS approval – see Q3)</u>?** If you answer 'Yes' to Q5 University ethical approval is required If you require advice on human biological material please contact Human Tissue Act (HTA) Designated Individual: Dr Sue Boyce [s.g.boyce@bradford.ac.uk] on ext 5897 or visit www.ethicaltissue.org	Yes ❒ No ❒
Q5a	If you answered 'Yes' to Q5, is the human material over 100 years old and archaeological? If 'YES' please refer to the Biological Anthropology Research Centre (BARC) guidelines at http://www.barc.brad.ac.uk/BARC_human_remains_policy.pdf	Yes ❒ No ❒
If you answer 'No' to Q5 and have answered 'No' to Q2, Q3 and Q4 ethical approval is <u>not</u> required.		

PLEASE COMPLETE and SIGN *<u>ONE</u>* of the two boxes below
*(in the case of a student project, we do require a **Supervisor's signature** in whichever box is relevant, before we can have the checklist signed off by the Research Ethics Panel):*

1. I have discussed this project with my student AND/OR
2. I confirm that there are **<u>no ethical issues</u>** requiring further consideration.

(Any subsequent changes to the nature of the project will require that the Panel are informed of all changes)

Signed by (Principal Investigator or Principal Supervisor (in case of student project))**:**

Signature: …… ……. Date: ……

PLEASE PRINT NAME
……

OR

I confirm that there are **ethical issues** requiring further consideration and will either:
1. refer the proposal to Ethical Tissue, or,
2. fill in and submit a full ethics application to be considered by the appropriate Research Ethics Panel.

Name (Principal Investigator/Principal Supervisor):

Signature: …….. **Date:** ……

PLEASE PRINT NAME
……..

Annex 1

Ethical Scrutiny by a University Research Ethics Panel is not required if:

- **The project is NOT a research project. There may be occasions where a project is not defined as research but still raises ethical issues – please submit for review if you think this is the case.**

- **The research project will only involve unlinked or aggregated human data which was collected and which was, at the time, subject to relevant research ethics panel approval.**
  However, where this is the case the researcher should at least confirm this in an email to the Research Support Unit's Ethics Administrator so that the Ethics Administrator has a record and can inform the Chair of the appropriate Research Ethics Panel that the researcher plans to go ahead without ethics approval. The email should confirm that the research project does not require ethics approval because it only involves unlinked or aggregated data, which when originally obtained from people was obtained in accordance with the protocol as approved at the time by an appropriate research ethics panel. The email should also briefly explain how the researcher now plans to use the unlinked or aggregated data.

- **The research is Public Domain Data:**

The Economic and Social Research Council's (ESRC) Research Ethics Framework states that ethics approval may not be required for data sets that exist in the public domain (e.g. datasets that are available from the Office for National Statistics or from the ESRC's Data Archive) so long as the appropriate permissions from individuals have already been obtained (i.e. informed consent) and where it is not possible to identify the individuals from the information provided. It must be remembered that public domain data is still covered by the laws of copyright.

- **The research involves Simple Uncontentious Questionnaires:**
  If a research project's only involvement with human subjects is a simple brief questionnaire with uncontroversial content it may not require ethical approval. It is the Principal Investigator or Principal Supervisor's responsibility to decide whether a project comes under this category and must indicate this at Q.4 on the checklist and attach the questionnaire document for information.

Guidance on supervisor and principal investigator sign off of uncontentious research

Audit and service evaluation are usually uncontentious, and guidance on how to differentiate between research, audit and service evaluation is given at: University Ethics website.

Even where a project is clearly research, as a supervisor or principal investigator, you can sign off simple, ethically uncontentious projects as not needing further ethical scrutiny. To do this, you should consider the level of risk to participants and researchers, the level of effort required by participants, the level of intrusion into participants' lives and the level of sensitivity of both the general subject matter and the information requested of participants. Basically, the lower these levels, the more likely the research is to be uncontentious and the more confident you should feel about signing off.

The following examples may help.

These studies can almost always be signed off by the supervisor or principal investigator:

- Brief questionnaires asking opinions about matters which are clearly not sensitive (attitudes to a product, beliefs about the usefulness of a course).
- Brief interviews about such topic.

- Observational studies about everyday behaviour in public places which involve no risk to subjects or the researcher.

But the following studies almost always need further scrutiny by a University Ethics Panel:

- Long questionnaires (these require considerable potential inconvenience to subjects).
- Long interviews
- Any questionnaires which ask subjects about intimate behaviours or issue likely to cause distress or would in other ways normally be regarded as contentious or sensitive (e.g. illegal activities, attitudes to abortion, capital punishment, immigration, euthanasia).
- Any interviews which examine these matters.
- Observational studies which involve intimate behaviours, behaviours which are not normally public or which might normally be considered contentious or sensitive (Activities of ethics committees, appointment committees, etc; professional consultations).

Naturally, this list is for illustration only, and should not be considered in any way exhaustive, permissive or prescriptive. For example, there are many categories of research not mentioned here which would definitely require ethics approval (e.g. treatment research). Rather the list demonstrates the issue of proportionality. Thus, even though the method may be the same for activities requiring and not requiring further scrutiny, the ***content*** in some way distinguishes between the two categories.

At the same time, there is obviously some middle ground. Are ethics committees not public? Is what is discussed so sensitive that the proposal needs further scrutiny? What about asking people about their views on the actions of senior members of staff in their organisation? Probably, it is in these middle ground areas that further advice should be sought from a Panel Chair about whether the project can be signed off by the supervisor or principal investigator alone. Given that, in so doing, the supervisor or PI is attesting to the ethical probity of the study, it is usually best to err on the side of caution where there is uncertainty. Panel chairs are very happy to advise.

(**Dr Martin Brinkworth**, Chair, Biomedical, Natural, Physical and Health Sciences Research Ethics Panel, m.h.brinkworth@bradford.ac.uk, ext. 3584

Dr Clare Beckett, Chair, Humanities, Social and Health Sciences Research Ethics Panel, c.beckett@bradford.ac.uk, ext. 3521)

Please submit this checklist to:

Ethics Administrator, RKTS,

F.24 Richmond Building

in hard copy or by email to

ethics@bradford.ac.uk

Appendix 4
NHS R&D Form IRAS Version 5.3.0

Welcome to the Integrated Research Application System
IRAS Project Filter
The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications. **Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.**
Please enter a short title for this project (maximum 70 characters) **Assessing the risk of Chemotherapy toxicity and hospital admission**
1. Is your project research? **Yes** ○ **No** ◉
2. Select one category from the list below: **Clinical trial of an investigational medicinal product□Clinical investigation or other study of a medical device□Combined trial of an investigational medicinal product and an investigational medical device□Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice Basic science study involving procedures with human participants** **Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology** **Study involving qualitative methods only** **Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)**

Study limited to working with data (specific project only) Research tissue bank□Research database

If your work does not fit any of these categories, select the option below:

Other study

○ ○ ○ ○ ○ ○ ○ ○ ◉ ○ ○ ○

2a. Please answer the following question(s):

a) Will you be processing identifiable data at any stage of the research (including in the identification of participants)?

Yes No

◉ ○

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

England Scotland□Wales□Northern Ireland

☑ ☐ ☐ ☐

3a. In which country of the UK will the lead NHS R&D office be located:

◉

England□Scotland□Wales□Northern Ireland□This study does not involve the NHS

○ ○ ○ ○

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

IRAS Form□NHS/HSC Research and Development offices□Social Care Research Ethics Committee□Research Ethics Committee□Confidentiality Advisory Group (CAG)□National Offender Management Service (NOMS)

(Prisons & Probation)

☐ ☑ ☐ ☐ ☐ ☐

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

It looks like your project is research requiring NHS R&D approval but does not require review by a REC within the UK Health Departments Research Ethics Service – is that right?

Yes No

◉ ○

4b. Please confirm the reason(s) why the project does not require review by a REC within the UK Health Departments Research Ethics Service:

Projects limited to the use of samples/data samples provided by a Research Tissue Bank (RTB) with generic ethical approval from a REC, in accordance with the conditions of approval.

Projects limited to the use of data provided by a Research Database with generic ethical approval from a REC, in accordance with the conditions of approval.

Research limited to use of previously collected, non-identifiable information Research limited to use of previously collected, non-identifiable tissue samples within terms of donor consent Research limited to use of acellular material

Research limited to use of the premises or facilities of care organisations (no involvement of patients/service users as participants)

Research limited to involvement of staff as participants (no involvement

of patients/service users as participants)

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5. Will any research sites in this study be NHS organisations?

Yes No

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5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

Yes No

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Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

Yes No

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The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

Yes No

○ ◉

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

Yes No

○ ◉

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

Yes No

○ ◉

9. Is the study or any part of it being undertaken as an educational project?

Yes No

Please describe briefly the involvement of the student(s):□Student is the main researcher. The student also works in the NHS trust and has access to the data as part of the trust role.

◉ ○

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ ○

Yes No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Yes No

○ ◉

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes No

○ ◉

NHS/HSC R&D Form (project information)

Please refer to the Submission and Checklist tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms) Assessing the risk of Chemotherapy toxicity and hospital admission

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Assessing the risk of Chemotherapy toxicity and hospital admission due to chemotherapy toxicity. Using patient reported toxicity after the first cycle of chemotherapy to develop a predictor of toxicity and hospital admission.

A2-1. Educational projects

Name and contact details of student(s):

Student 1

Address

Post Code E-mail Telephone Fax

Title Forename/Initials Surname Mr Samuel Malton

Nottingham City Hospital Hucknall Road Nottingham NG51PB samuel.malton@nuh.nhs.uk 01159691169

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree: DPharm

Name of educational establishment: University of Bradford

Name and contact details of academic supervisor(s):

Academic supervisor 1

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Please state which academic supervisor(s) has responsibility for which student(s):

Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s) Academic supervisor(s) Student 1 Mr Samuel Malton

Dr Jonathan Silcock

Address

Post Code E-mail Telephone Fax

Title Forename/Initials Surname Dr Jonathan Silcock

University of Bradford Great Horton Rd Bradford BD71DP J.Silcock@bradford.ac.uk

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

Student□Academic supervisor Other

○ ◉ ○

A3-1. Chief Investigator:

Post

Qualifications

Employer Work Address

Post Code□Work E-mail□* Personal E-mail□Work Telephone□* Personal Telephone/Mobile Fax

Title Forename/Initials Surname Dr Jonathan Silcock

Senior Lecturer in Pharmacy Practice

MRPharmS FHEA□PHD

MSc□University of Bradford Great Horton Rd Bradford

BD71DP j.silcock@bradford.ac.uk

01274 236624

**** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.□A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.***

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Appendix 4

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A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project? ***This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.***

Address

Post Code E-mail Telephone Fax

Title Forename/Initials Surname Mrs Tamsin Holt

University of Bradford Great Horton Road Bradford BD71DP t.l.holt@bradford.ac.uk 01274 235184

A5-1. Research reference numbers. ***Please give any relevant references for your study:*** **Applicant's/organisation's own reference number, e.g. R & D (if**

available):

Sponsor's/protocol number:

Protocol Version:

Protocol Date:

Funder's reference number:

Project website:

Additional reference number(s):

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.

Ref.Number Description Reference Number

A5-2. Is this application linked to a previous study or another current application?

Yes No

Please give brief details and reference numbers.

○ ◉

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. ***Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.***

At Nottingham University Hospitals, a new service has been established involving a nurse led call back service to all oncology patients receiving chemotherapy. Patients receive a call back 24 hours after their first cycle of chemotherapy

and undergo a full toxicity assessment over the telephone. Data is collected around toxicity, which will be used to look at the factors that can be used to predict chemotherapy toxicity and the risk of hospital admission from toxicity.

A6-2. Summary of main issues. ***Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.***

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to

participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Few significant issues are raised as data is collected as part of a service provided by the NHS trust. Data can be anonymised before manipulation. There is the potential that services may be changed as a result of any findings of the study. If a toxicity predictor is developed it could be used to inform clinicians of the treatment to offer patients. Any predictor developed would be thoroughly tested and any recommendations made from the research will be well though out and evidence based. If more research is required to validate any findings then this will be stated. Any changes to services within the trust will follow trust policy and procedure and will be reviewed by relevant committees.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

Case series/ case note review☐Case control☐Cohort observation☐Controlled trial without randomisation Cross-sectional study

Database analysis☐Epidemiology☐Feasibility/ pilot study☐Laboratory study☐Metanalysis☐Qualitative research☐Questionnaire, interview or observation study Randomised controlled trial

Other (please specify)

☐ ☐ ☑ ☐ ☐ ☑ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

What risk factors can be used to predict chemotherapy toxicity? What is the risk of hospital admission for toxicity with chemotherapy? Can a tool be developed to predict this?

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Little evidence is available around overall general chemotherapy toxicity and the risk of it. There is also little data available around the risk of hospital admission for chemotherapy toxicity, despite admission being a common consequence of toxicity. Admission is a negative thing for both patient and healthcare provider and it is thought that if this can be predicted it can either be managed or avoided. A literature search has helped to identify many negative

effects of chemotherapy toxicity, meaning that a greater understanding of the risk of toxicity, which this research aims to provide, will be very valuable. A 2008 UK report looked at deaths within 30 days of receiving systemic anti-cancer therapy (SACT). It was noted that 43% of patients who had died within 30 days of receiving SACT had experienced a grade 3 or 4 toxicity according to CTCAE (common terminology criteria for adverse events) criteria related to their treatment (Mort, D., Lansdown, M., Smith, N., Protopapa, K., & Mason, M. (2008, October 3). For better, for worse? Retrieved March 11, 2015, from http://www.ncepod.org.uk/2008report3/Downloads/SACT_report.pdf). An observational study in a London hospital found that early treatment discontinuation was required in 21.3% of elderly patients receiving chemotherapy for various cancers due to toxicity(Kalsi, T., Babic-Illman, G., Fields, P., Hughes, S., Maisey, N., Ross, P., *et al*. (2014). The impact of low-grade toxicity in older people with cancer undergoing chemotherapy, 111(12), 2224–2228. http://doi.org/10.1038/bjc.2014.496).

A 2005 breast cancer trial was forced to close a high dose arm early due to toxicity (Brain, E., Levy, C., Serin, D., Roché, H., Spielmann, M., Delva, R., *et al*. (2011). High rate of extra-haematological toxicity compromises dose-dense sequential adjuvant chemotherapy for breast cancer. British Journal of Cancer, 105(10), 1480–1486. http://doi.org/10.1038/bjc.2011.414). High rates of skin toxicity (32.4% rate of grade 3 /4 toxicity) were reported in the high dose arm of this randomized phase II trials which investigated the sequential approach of anthracycline and taxane based adjuvant chemotherapy in patients with high risk breast cancer. This study highlights the problematic nature of toxicity and highlights the potential effects on trials and potentially curative chemotherapy. This research aims to identify the risk factors for toxicity so that these can be considered when making prescribing

decisions.

A13. Please summarise your design and methodology. ***It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.***

A service is now in place at Nottingham University Hospitals whereby all oncology patients who receive their first chemotherapy, will receive a phone call the following day by a nurse to assess any side effects. Toxicity is systematically reviewed and recorded in a pre-defined database. Patient factors are recorded such as age, disease, performance status and records are made of the chemotherapy given. Once data has been collected for a full year as part of the existing service, it will be anonymised and used for research purposes. It will be collected by nurses at Nottingham University Hospitals (NUH) and patient identifiable data will only be available to members of the oncology team at NUH. Any data used for research will have patient identifiers removed. Multivariate analysis will be performed on the data to look at what factors can be used to predict the risk of toxicity. The data will be compared with the hospital admissions data and the risk of hospital admission from chemotherapy toxicity will be calculated.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

Blood Cancer Cardiovascular Congenital Disorders Dementias and Neurodegenerative Diseases Diabetes Ear Eye Generic Health Relevance Infection Inflammatory and Immune System Injuries and Accidents Mental Health

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Metabolic and Endocrine Musculoskeletal Neurological Oral and Gastrointestinal Paediatrics

Renal and Urogenital Reproductive Health and Childbirth Respiratory Skin Stroke

Gender: Lower age limit: 18 Upper age limit:

Male and female participants Years Years

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A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Adult patients (over 18 years old) Patients with a diagnosis of a solid tumour cancer Patients who have undergone a first cycle of chemotherapy at Nottingham University Hospitals (NUH) as an outpatient Patients who were able to have a toxicity assessment performed over the telephone

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Any paediatric patients Any patient receiving chemotherapy classed as an inpatient regimen at NUH Any patient receiving chemotherapy as part of a clinical trial Any patient who was not able to have toxicity assessed the day after chemotherapy or who could not be contacted

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example,*

identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Details of all toxicity assessments are recorded in an NUH excel spreadsheet. Patients who have undergone the pre- defined treatment the day before are identified by automatic report run by the chemotherapy electronic prescribing system "Chemocare". All data is recorded and processed by the team providing the service.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

Yes No

Please give details below:

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A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ ◉

Yes No

A29. How and by whom will potential participants first be approached?

Participants will not be approached by the research team but will receive a phone call as part of the service offered by NUH. The phone call will be from the Chemotherapy action team nurse.

A30-1. Will you obtain informed consent from or on behalf of research participants?

Yes No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

If you are not obtaining consent, please explain why not.

Data is collected as part of an NHS chemotherapy service. Any data used at the point of research will be anonymised. Only NUH employees directly involved in the care of chemotherapy patients will have access to any identifiable data.

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Please enclose a copy of the information sheet(s) and consent form(s).

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

Access to medical records by those outside the direct healthcare team Access to social care records by those outside the direct social care team Electronic transfer by magnetic or optical media, email or computer networks Sharing of personal data with other organisations□Export of personal data outside the EEA□Use of personal addresses, postcodes, faxes, emails or telephone numbers Publication of direct quotations from respondents□Publication of data that might allow identification of individuals□Use of audio/visual recording devices□Storage of personal data on any of the following:

Manual files (includes paper or film) NHS computers□Social Care Service

computers Home or other personal computers University computers

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Private company computers

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Laptop computers

Further details:

The toxicity database will be stored on NHS computers only and the only patient identifier will be the NHS number. Members of the Nottingham University Hospitals Acute Oncology Team will be the only people to have access to this data. It will be extracted into a separate spreadsheet for research purposes, at which point it will be anonymised and the NHS number removed.

A37. Please describe the physical security arrangements for storage of personal data during the study?

This will be done in accordance will NUH policy around data protection. Only NUH staff will be able to access any identifiable data.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

The only identifier used in the database will be the NHS number. Only NUH staff who are bound by confidentiality policy will have access to identifiable data, to which access is restricted. At the point of data manipulation identifiers will be removed, making all data anonymous.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Only NUH employees directly involved in the care of chemotherapy patients.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

A combination of on NHS computers and personal laptop only once data has any identifiers removed. All data will be analysed by the student who is also an employee of NUH and directly involved in the care of chemotherapy patients.

A42. Who will have control of and act as the custodian for the data generated by the study?

Post Qualifications Work Address

Post Code Work Email Work Telephone Fax

Title Forename/Initials Surname Mr Samuel Malton

Advanced Pharmacy Practitioner, oncology

MPharm PGCert PGDip MSc

Nottingham City Hospital Hucknall Road Nottingham NG51PB samuel.malton@nuh.nhs.uk 01159691169

A43. How long will personal data be stored or accessed after the study has ended?

○ **Less than 3 months**

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○ **3 – 6 months 6 – 12 months 12 months – 3 years Over 3 years**

If longer than 12 months, please justify:

The service introduced is likely to be on-going and as such continuous

data collection and review will occur for the purposes of service review.

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A44. For how long will you store research data generated by the study?

Years: 5 Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

Any patient data will be stored on NHS computers with only NUH staff able to access, in accordance with NUH policy. Anonymised data will be stored for 5 years as indicated above.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

Yes No

○ ◉

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

Yes No

○ ◉

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

Yes No

If yes, please give details including the amount of any monetary payment or the basis on which this will be calculated:

Employee of Nottingham University Hospitals

◉ ○

NOTIFICATION OF OTHER PROFESSIONALS

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

Yes No

Please give details, or justify if not registering the research.

Unaware of an appropriate public database on which to register research. Will be registered at the University of

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Bradford and Nottingham University Hospitals.

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study?*Tick as appropriate:*

Peer reviewed scientific journals Internal report Conference presentation Publication on website

Other publication

Submission to regulatory authorities

Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators

No plans to report or disseminate the results Other (please specify)

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A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

No identifiable data will be published

A53. Will you inform participants of the results?

Yes No

Please give details of how you will inform participants or justify if not doing so.

Data is not patient identifiable and patients do not consent to being included in the research as mentioned above. This would make it impossible to trace patients to be able to inform them of results.

○ ◉

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed?*Tick as appropriate:*

Independent external review Review within a company Review within a multi−centre research group Review within the Chief Investigator's institution or host organisation Review within the research team Review by educational supervisor Other

***Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:*Discussion with several clinicians from different disciplines within NUH around the purpose of and reason**

for research and the chosen methodology.

Discussion and review with academic supervisor at University of Bradford.

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For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed?*Tick as appropriate:*

Review by independent statistician commissioned by funder or sponsor Other review by independent statistician Review by company statistician Review by a statistician within the Chief Investigator's institution

Review by a statistician within the research team or multi−centre group

Review by educational supervisor

Other review by individual with relevant statistical expertise

No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

☐ ☐ ☐ ☐ ☐ ☑ ☐ ☐

Department Institution Work Address

Post Code Telephone Fax Mobile E-mail

a.j.scally@bradford.ac.uk

Title Forename/Initials Surname

Dr Andy School of Life Sciences University of Bradford University of

Bradford Great Horton Rd Bradford BD71DP **Scally**
Please enclose a copy of any available comments or reports from a statistician.
A57. What is the primary outcome measure for the study? **The rate of toxicity form chemotherapy and the rate of hospital admission due to toxicity**
A58. What are the secondary outcome measures?*(if any)*
A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.* **Total UK sample size: 1500 Total international sample size (including UK): Total in European Economic Area:** ***Further details:***

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A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

This is the possible number of patients who may receive a first cycle of chemotherapy at NUH within one year. The actual number may be more but it is expected that the research may focus on specific tumour sites.

A61. Will participants be allocated to groups at random?

Yes No

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A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The mean and median number of toxicities experienced will be calculated along with the mean number of instances of hospital admission. The research will aim to produce hazard ratios for specific toxicity and for hospital admission.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. ***Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.***

Post Qualifications

Employer Work Address

Post Code Telephone Fax Mobile Work Email

Title Forename/Initials Surname Dr Eleanor James

Consultant clinical oncologist

MBCHB FRCR

Nottingham University Hospitals Nottingham City Hospital Hucknall Rd Nottingham

NG51PB

eleanor.james@nuh.nhs.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status: ○ ○**NHS or HSC care organisation Academic**

Pharmaceutical industry Medical device industry Local Authority

Commercial status: Non- Commercial

◉ ○ ○ ○

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○

Other social care provider (including voluntary sector or private organisation)

Other

If Other, please specify:

○

Contact person

Name of organisation Given name□Family name Address

Town/city Post code

Country

Telephone Fax E-mail

University of Bradford□Tamsin□Holt□University of Bradford, Great Horton Rd Bradford

BD71DP□UNITED KINGDOM

t.l.holt@bradford.ac.uk

Is the sponsor based outside the UK?

Yes No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

○ ◉

A65. Has external funding for the research been secured?

Funding secured from one or more funders□External funding application to one or more funders in progress No application for external funding will be made

What type of research project is this?□Standalone project□Project that is part of a programme grant□Project that is part of a Centre grant□Project that is part of a fellowship/ personal award/ research training award Other

Other – please state:

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A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

Yes No

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A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another

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country?

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Yes No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Organisation Address

Post Code Work Email Telephone Fax

Mobile

Title Forename/Initials Surname Ms Charlotte Davies

Nottingham University Hospitals□Nottingham Integrated Research Centre, C-Floor Queens Medical Centre□Nottingham□NG72UH□rdappl@nuh.nhs.uk□01159249924

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Plannedstartdate: 01/01/2015 Planned end date: 31/12/2016 Total duration:

Years: 1 Months: 11 Days: 31

A71-1. Is this study?

Single centre Multicentre

◉ ○

A71-2. Where will the research take place? *(Tick as appropriate)*

England□Scotland□Wales□Northern Ireland□Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

Yes No

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A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑

NHS organisations in England□NHS organisations in Wales□NHS organisations in Scotland□HSC organisations in Northern Ireland GP practices in England

GP practices in Wales□GP practices in Scotland□GP practices in Northern Ireland

Joint health and social care agencies (eg community mental health teams)

Local authorities Phase 1 trial units Prison establishments Probation areas

Independent (private or voluntary sector) organisations

Educational establishments Independent research units Other (give details)

1

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Total UK sites in study: 1

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

Yes No

○ ◉

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

NUH and University of Bradford policy. Regular review on a monthly basis of research project with academic supervisor.

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

NHS indemnity scheme will apply (NHS sponsors only)☐Other insurance or indemnity arrangements will apply (give details below)

☐ ☑

University of Bradford is the research sponsor. Professional indemnity and public liability insurance are in place. The certificates can be found at the following link: http://www.bradford.ac.uk/finance/financial-information/in surance/liability-insurance/

There is no patient participation in this research which is solely based on data collected as part of a service and so no potential for patient harm arising from research activity.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

NHS indemnity scheme will apply (protocol authors with NHS contracts only) Other insurance or indemnity arrangements will apply (give details below)

University of Bradford is the research sponsor. Professional indemnity and public liability insurance are in place. The certificates can be found at the following link: http://www.bradford.ac.uk/finance/financial-information/in surance/liability-insurance/

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Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will

be made at these sites and provide evidence.

NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only) Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

University of Bradford is the research sponsor. Professional indemnity and public liability insurance are in place. The certificates can be found at the following link: http://www.bradford.ac.uk/finance/financial-information/in surance/liability-insurance/

_____ ___ ☐ ☑

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

Yes ○ **No** ○ **Not sure**

◉

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. ***For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.***

Research site

Institution name Department name Street address Town/city

Post Code

Nottingham University Hospitals Oncology/Pharmacy Hucknall Rd Nottingham

NG51PB

Investigator/ Collaborator/ Contact

Title Mr

First name/ Initials

Samuel Surname Malton

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PART D: Declarations

D1. Declaration by Chief Investigator

1. **The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.**
2. **I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.**
3. **If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.**
4. **I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.**
5. **I undertake to submit annual progress reports setting out the**

progress of the research, as required by review bodies. □

6. **I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.** □

7. **I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.** □

8. **I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.** □

9. **I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:** □**Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.** □**May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.** □**May be seen by auditors appointed to undertake accreditation of RECs (where applicable).** □**Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.** □**May be sent by email to REC members.** □

10. **I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.** □

11. **Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact**

point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)* *NRES would like to include a contact point with the published summary of the study for those wishing to seek further*

information. We would be grateful if you would indicate one of the contact points below.

Chief Investigator

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Sponsor Study co-ordinator Student Other – please give details None

Access to application for training purposes *(Not applicable for R&D Forms) Optional – please tick as appropriate:*

I would be content for members of other RECs to have access to the information in the application in confidence

for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Dr Jonathan Silcock on 16/05/2016 12:27.

Job Title/Post: Organisation: Email:

Senior Lecturer in Pharmacy Practice University of Bradford j.silcock@bradford.ac.uk

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D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. **This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.** □
2. **An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.** □
3. **Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.** □
4. **Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.** □
5. **Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.** □
6. **The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.** □**Please note:** ***The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*** □
7. **Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.** □
8. **Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA**

still applies. □

Signature: ..... Print Name:

Post: Organisation:

Date: ***(dd/mm/yyyy)***

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D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by Dr Jonathan Silcock on 16/05/2016 12:27.

Job Title/Post: Organisation: Email:
Senior Lecturer in Pharmacy Practice University of Bradford j.silcock@bradford.ac.uk

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Appendix 5

Literature Search Strategy

Medline and Embase were both used as the databases of choice for the literature search. Where possible controlled vocabulary, thesaurus or MeSH search terms were used, however if these yielded no results it was sometimes necessary to broaden the search.

Randomised Controlled trials from well known international journals were the literature of choice, however when these brought no results smaller scale studies were sought from lesser known journals. Only articles available in English were included. Once articles were identified, the bibliographies were inspected in order to identify any other useful information.

To begin with, literature around the incidence and prevalence of chemotherapy toxicity in general was sought using the following terms:

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + prevalence

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + incidence

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + admission (hospitalisation)

The economic effects of chemotherapy toxicity were also of interest as well as the impact on the services managing these patients. To look at this the following search terms were used:

Chemotherapy / antineoplastic + Costs (Healthcare costs, Drug costs, Costs of illness, Hospital Costs) + toxicity (drug related side effects and reactions)

More general searching around chemotherapy and cost yielded more data around the economic and also other consequences of toxicity.

A search was performed to look at the risk of admission from chemotherapy toxicity using the following terms:

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + admission (hospitalisation)

This proved difficult and the search terms were broadened which did not identify any relevant data. More general data around hospital admission was sought using:

Admission (hospitalisation) + predictors

Admission (hospitalisation) + risk factors

The next area to focus the search was around predicting toxicity. The following terms were used:

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + risk

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + risk factors

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + prediction

The next area of interest was any patient factors that may have been identified as playing a role in toxicity. A general search was undertaken using the following:

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + patient factors

The results from this were difficult to process as much literature was identified. Search terms were therefore made more specific in order to filter the results:

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + age (age groups/age factors)

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + Karnofsky performance status.

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + ECOG performance status.

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + co-morbidity

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + social class

The next area to look at was any literature regarding measures to protect from overall toxicity.

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + primary prevention

It was then decided to look at the more common individual cancers:

Breast Cancer

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + breast neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + incidence + breast neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + prevalence + breast neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + (hospitalisation) + breast neoplasms

Lung Cancer

The following terms were used to assess the literature around toxicity in lung cancer.

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + lung neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + incidence + lung neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + prevalence + lung neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + (hospitalisation) + lung neoplasms

Colorectal Cancer

The same search strategy was employed for colorectal cancer.

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + colorectal neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + incidence + colorectal neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + prevalence + colorectal neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + (hospitalisation) + colorectal neoplasms

Prostate Cancer

Similar search terms were used for prostate cancer.

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + prostate neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + incidence + prostate neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + prevalence + prostate neoplasms

Chemotherapy / antineoplastic + toxicity (drug related side effects and reactions) + (hospitalisation) + prostate neoplasms

Literature around individual toxicities was then investigated:

Nausea and Vomiting

Chemotherapy / antineoplastic + nausea + vomiting + prevalence

Chemotherapy / antineoplastic + nausea + vomiting + incidence

Chemotherapy / antineoplastic + nausea + vomiting + risk

Chemotherapy / antineoplastic + nausea + vomiting + admission (hospitalisation)

Diarrhoea

The following terms were used to identify literature around patients with experiencing diarrhoea with chemotherapy:

Chemotherapy / antineoplastic + diarrhoea + prevalence

Chemotherapy / antineoplastic + diarrhoea+ incidence

Chemotherapy / antineoplastic + diarrhoea + risk

Chemotherapy / antineoplastic + diarrhoea + admission (hospitalisation)

Skin Reactions

To identify the literature around skin reactions with chemotherapy, the following search terms were employed:

Chemotherapy / antineoplastic + drug related side effects and adverse reactions + skin + prevalence

Chemotherapy / antineoplastic + drug related side effects and adverse reactions + skin + incidence

Chemotherapy / antineoplastic + drug related side effects and adverse reactions + skin + risk

Chemotherapy / antineoplastic + drug related side effects and adverse reactions + skin + admission (hospitalisation)

Fatigue

Chemotherapy / antineoplastic + drug related side effects and adverse reactions + fatigue + prevalence

Chemotherapy / antineoplastic + drug related side effects and adverse reactions + fatigue + incidence

Chemotherapy / antineoplastic + drug related side effects and adverse reactions + fatigue + risk

Chemotherapy / antineoplastic + drug related side effects and adverse reactions + fatigue + admission (hospitalisation)

The above search did not bring many results, so broader terms were used to search around fatigue.